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Editorial

Initial Events in Cardiogenesis

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Before discussing some of those events which have been observed in the development of the avian heart, I should like to recall the classic experiment of Aristotle which consisted of opening and examining hens' eggs of known incubation time. On the first and second days of incubation, the development which would have been visible to Aristotle's unaided eye consists almost entirely of the growth of the yolk sac and extraembryonic somatopleure over the surface of the yolk mass. But on the third day, Aristotle noted a centrally located, pulsating, red speck which subsequently was named the *punctum saliens*. Aristotle recognized this small pulsating "blood spot" as the beginning of the heart and, in a departure from objectivity, theorized that it was the early manifestation of the soul, which he considered as a special quality of the heart. It is of profound significance to a student of embryology that Aristotle saw the small, pulsating speck and associated it with the larger and more complex heart of the hatched bird. It is meaningful also that he recognized the development of the heart as an epigenetic process, that is, a process of organogenesis which involves changes in the qualitative and quantitative complexity of the primordium and not a simple unfolding and growth of a preformed heart.

It has been found that by estimating and comparing the degrees of qualitative and quantitative complexity that arises in heart-forming cells, one can gain an appreciation of the sequence of events in the formation of the heart. Therefore, before an understanding of cardiogenesis can be obtained, we must have information on changes in the types and numbers of cells, on reorganizations of the spatial relationships that cells have with one another, and on reorganizations of the spatial relationships of subcellular constituents of heart-forming tissues. As will be evident from the discussion, some of the pieces of a conceptual model are at hand; a few of these pieces have been and are being fitted together.

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A MODEL OF CARDIOGENESIS

At the stage of development of the unincubated avian embryo there is a population of cells which, perhaps by virtue of the conditions of the ecological niches from which it arises and within which it grows and develops, is destined to differentiate into a coordinated complex of contractile elements, the heart. Upon incubation of the egg, these cells or their descendants are affected by movements that result in their localization in two bilateral groups of mesoderm which flank the anterior end of the embryo's primitive streak. As the brain, spinal cord, and somites of the embryo develop, some of the cells of each group become organized as a pair of bilateral cords lying between the mesoderm and the underlying entoderm. Gradually, these cords hollow out to form a pair of endocardial tubes. The overlying mesoderm thickens and folds to form troughs of epimyocardium that lie inverted over the tubes. Then, the epimyocardial troughs which contain the endocardial tubes migrate medially in pace with the splanchnopleuric foldings which form the foregut floor. Upon becoming apposed in the midline, the tubes and troughs join to form the double-walled tubular heart. All of this happens during the first 30 hours of incubation. Within 2 or 3 hours after the bilateral heart primordia have fused at the ventricular level, the heart twitches for a short time and then begins to beat rhythmically. Fluid which contains blood cells commences to rush through the heart and blood vessels in a life-giving flow that, normally, will not pause or cease until death, not even during the extensive remodeling process that converts the simple tube to the four-chambered heart.

From the reference point which this general model provides, let us proceed toward obtaining an understanding of the initiation of the formation of the heart. If one cuts into fragments an embryo wherein no neural tissue, heart tissue, or any other types of adult tissue have differentiated, and grows these fragments separately in tissue culture or on the chorioallantoic membranes of older embryos, the fragments differentiate into a wide range of typical adult tissues. By keeping account of the ages of the embryos used and the sites of origin of the fragments, one can project back to its origin the differentiational end point of each fragment. The assemblage of such information has produced the maps of organ-forming areas that are used today in teaching and research.

From these studies, it has been found that the cells which have the ability to differentiate into heart reside in a peripheral band of tissue which is circumferential to the embryonic shield of the unincubated blastoderm. Studies of this kind have not been carried out on eggs removed from the genital tract; hence, the earliest appearance of cardiogenic ability in the avian embryo is unknown. It would be interesting to know whether the entire blastoderm of the oviducal egg has cardiogenic ability or whether this capacity arises only in the peripheral cells. It may be that cells develop this ability very early and shift to the periphery of the blastoderm before the egg is laid. Such shifts are well known in subsequent stages of development, for, when the primitive streak forms, the cardiogenic cells become segregated to the posterior two thirds of the embryo. From this position, the cardiogenic cells, and other cells which have a mesodermal fate, converge upon the primitive streak and traverse it in order to attain positions

between the ectodermal and entodermal layers. Completion of these movements is followed by the extension of the mesodermal layers laterally and anteriorly, so that, at the termination of the streak stage, the cardiogenic cells arrive at the definitive positions at which they differentiate into the bilateral cardiac primordia. The development of cardiac tissue from certain isolated fragments of the early embryo is taken to mean that the capacity for cardiogenesis arises very early in the embryo, and that if reflects fundamental steps in the epigenesis of this type of tissue. A study of the chemical differentiation of heart-forming cells is an approach toward the identification and understanding of these steps.

A number of years ago, a hypothesis was put forth proposing that organs and tissues could be recognized by their specific proteins. The application of the tools of immunology to this theory revealed that animal tissues are antigenic and evoke the production of specific antibodies when injected into a rabbit or some other suitable animal. One of the earliest applications of this tool to the study of embryogenesis was made by James D. Ebert, now the Director of the Department of Embryology of the Carnegie Institution of Washington. Ebert cultured early embryos on media containing antibodies against adult chicken heart and brain, and observed that (1) embryos cultured on media containing control sera developed normally, and that (2) embryos cultured on media containing antibrain and antiheart antisera had defective brains and hearts, respectively. From this and related studies, it was apparent that the synthesis of tissue-specific antigens is an integral part of epigenesis, and that the identification and study of antigens in the developing heart would constitute an effective approach to an understanding of the formation of the heart.

In preparation for such studies on embryos, Dr. Ebert and his co-workers used as antigens the purified adult heart proteins, myosin and actin. Antisera obtained against these antigens were absorbed with skeletal myosin and actin to provide antibodies with high specificity for heart. Detection of myosin and actin in the embryos was made by combining in precipitin tests extracts of fragments of embryos and the highly specific antisera. The results of the precipitin tests provide an index to the myosin- and actin-containing areas during development.

The correlation of information on the locations of myosin and actin in embryos with our knowledge of the locations of heart-forming cells has indicated several noteworthy relationships. First of all, the heart-forming cells of the prestreak embryo do not synthesize the proteins myosin and actin. Their capacity to synthesize myosin arises only after they have begun to traverse the primitive streak and to take positions between the ectoderm and entoderm. Secondly, once the synthesis of myosin begins, its location corresponds to the areas of heart-forming cells. It should be recalled from the studies on the location of heart-forming cells that the heart-forming capacity gradually becomes segregated to and concentrated in bilateral, mesodermal areas which flank the anterior end of the primitive streak. It is in these same regions that the centers of the highest concentration of myosin localize. The third, and last, relationship is that, once the heart-forming capacity and myosin are restricted to these bilateral areas, actin appears in the same areas. The recognition of these temporal and spatial

relationships of the capacity for heart formation, of the appearance of myosin and actin, and of the positional changes of the cells indeed contributes to our growing concept of cardiogenesis and suggests new possibilities for learning more. Currently, these possibilities are being realized in investigations of the metabolism of heart-forming cells, of the effects of surrounding cells on the differentiation of heart-forming cells, and of experimental cardiomyogenesis, the induction of cardiac muscle from noncardiogenic cells. It will be apparent from the study of the results from these investigations that these approaches are yielding data valuable to an understanding of the molecular events underlying cardiogenesis.

CAUSALITIES IN CARDIOGENESIS

It is probable that cardiogenesis is related to a specific type of intermediary metabolism and that this differentiates early in accompaniment with the onset of specific synthetic activities. From studies by Nelson Spratt, of the University of Minnesota, it has been posited that nutritional requirements and susceptibilities to metabolic inhibitors differ quantitatively from one set of histogenetic activities to another. One of the earliest findings made by Spratt showed clearly that certain low concentrations of sodium fluoride have a specific inhibitory effect on the heart. The author, in association with Dr. Ebert, extended this study to the heart-forming areas and found that, even at that early stage, the cardiogenic cells are differentially susceptible to fluoride. It should not be implied from results of this sort that a pattern of energy production has a causative effect on the genesis of a pattern of differentiation. Since final products of energy production, high energy phosphate bonds, supply indiscriminately any and all maintenance and developmental processes, such a possibility is unlikely. However, the possibility of a connection between two such processes may exist and should be investigated.

One of the events in the initiation of cardiogenesis which was mentioned earlier is the migration of heart-forming cells through the primitive streak in order to attain positions in the mesoderm. The appearance of myosin in the heart-forming cells has been correlated with this change in the environment of the cardiogenic cells. And so, it is pertinent to ask whether the environmental change has anything to do with the appearance of synthetic capacity.

From the observations which have been recorded thus far, there is good circumstantial evidence that involution of the cardiogenic cells does affect their differentiation. Direct evidence for such an effect is lacking. There is proof, however, from the laboratory of R. C. Fraser, at the University of Tennessee, that another system, cytochrome oxidase (indophenol oxidase), arises as a result of cellular migration through the primitive streak. Fraser found that this system appears in prospective mesoderm cells only after they have traversed the streak. Presumably, some of the involuting cells are cardiogenic, and the genesis of the cytochrome oxidase system may represent another facet of their differentiation.

We should recall also the powers of organization and induction that have been attributed to the primitive streak and primitive node. It is conceivable that these

powers include the organization of the heart-forming cells. Following this line of reasoning, the author and Robert McGrew studied recently the influence of the streak and adnexa on the differentiation of the bilateral heart-forming areas. This was done by making a longitudinal incision of the embryo at a distance of 0.1 to 0.3 millimeter parallel to the midline of the primitive streak. The resulting pieces, one associated with the node and streak and the other lacking these structures, were cultured separately in vitro on the surface of a semisolid medium. The development of pulsating hearts in these pieces was recorded after 30 hours of culture. The percentages of development of pulsating heart were 65, 70, 89, and 94 for pieces bearing node and streak from embryos of 16, 19, 22, and 25 to 30 hours of incubation, respectively. These values are comparable to the incidence of formation of pulsatile heart in intact embryos of the same age range. In contrast, the percentages of development of pulsatile heart in the pieces lacking node and streak were 12, 36, 91, and 94, respectively. Each determination of percentage was made from 47 or more observations. It is critical to recognize that the embryos used in this study had completed the morphogenetic movements which direct the heart-forming cells to their positions in the mesoderm. Hence, both pieces of embryos which result from the incision bear cells which have heart-forming capacity. The low percentages of development of pulsatile heart in pieces lacking the node and adnexa from 16- and 19-hour embryos may point to the absence of some stimulus for cardiogenesis. It is apparent from the data that such a possible stimulus is exerted before, and is certainly not needed after, the definitive primitive streak stage (18 to 19 hours of incubation), for no difference has been found in the percentage of formation of pulsatile heart in pieces from older embryos. It seems obvious from these results that axial development which involves the streak and node may in some way affect the differentiation of heart. How this is mediated is not resolved at this time.

Before we go on to the subject of experimental cardiomyogenesis, further reference to the ecology of heart formation should be noted. This concerns the proximity of the heart-forming cells to the entodermal layer which comes about as a result of their involution through the streak. From the late streak stages up to the stage of the development of the tubular heart, the heart-forming cells lie on the entoderm layer. When pieces of cardiogenic tissue from such embryos are trimmed of entoderm and cultured in tissue culture, their organization into pulsatile heart tissue is inferior to that of pieces on which the entoderm is retained. In amphibian embryos, the entodermal requirement for cardiogenesis is even more pronounced than that seen in avian embryos. Additional evidence which alludes to an influence of the entoderm on formation of the heart comes from the study of the effects on the chick embryo of antimycin A, a substance produced by the Streptomyces mold. While in association with Dr. Ebert at Indiana University, the author cultured early chick embryos on media containing tenths of a gamma per milliliter quantities of the antibiotic. Such embryos, grown with their *entodermal* surfaces contacting the medium, had their hearts and other mesodermal developments almost completely blocked. These experiments have been repeated successfully by John McKenzie, at the Department of Embryology of the Carnegie Institution of Washington. However, in another study, McKenzie

cultured the embryos with their *ectodermal* surfaces contacting the antimycin-containing media. In contrast to what had been observed earlier by the author, formation of the heart in these embryos was essentially normal but neural development was affected. These studies are to be interpreted cautiously, for it is clear that the portal of entry of an inhibitor into an embryo affects the final picture of inhibition. However, it is tempting to speculate that the absence of hearts in embryos cultured on their *entodermal* surfaces reflects an insufficiency of that layer to support cardiogenesis.

From the foregoing investigations, it is clear that the capacity for cardiogenesis arises very early in the embryo. Between the time when this capacity arises and the time of the moulding of the tubular heart, the cardiogenic cells begin to synthesize specific heart proteins. The onset of synthesis has been observed to coincide with or to follow immediately certain changes in the environment of the cardiogenic cells. Special metabolic proclivities may arise also in relation to these changes. The questions which come forth are: What happens in some of the early embryonic cells to make them capable of cardiogenesis? What causes these cells to develop this capacity? Can determinants for cardiogenesis be detected in the cardiogenic cells? Once this capacity for cardiogenesis arises in a cell, does it faithfully pass on the determinants for this capacity to its daughter cells at cell division? How do these determinants carry out or control processes of synthesis and energy production? How is the genesis and maintenance of cardiogenic capacity related to the changing environment of the cardiogenic cells?

Experimental designs and tools are being projected in an attempt to bring biochemical, immunochemical, genetic, and embryological information together and, hence, to open these questions to additional investigative approaches. Recent investigations already have yielded information that answers some of the questions posed above, as well as suggesting new experiments.

Within the past ten years, evidence has accumulated which supports the contention that the interaction of differentiating embryonic tissues is mediated by certain diffusable agents. Experiments which led to this view were incited mainly by the observations of Jean Brachet, of the University of Brussels, Belgium. Brachet's observations, which were recently summarized in his *Biochemical Cytology*, suggest that the diffusable agents are ribonucleic acids (RNA) or RNA-proteins. An account of recent studies by M. C. Niu, of the Rockefeller Institute, illustrates experimental tissue interaction. Niu cultured ectoderm from gastrula-stage amphibian embryos with extracts of calf kidney and found that the cells differentiated into tubule-like configurations. Similarly, ectoderm cells in extracts of calf thymus assumed a thymus-like organization. Niu has presented results which suggest that the active component of the extracts is RNA. The significance of these results to our topic is found in the knowledge of the synthesis of protein by microsomes (RNA-rich cytoplasmic granules), the infective capacity of viral RNA, and the possibility that a suitable animal RNA type of virus might in some way transfer RNA or RNA-protein from one cell to another. From this background of information, Dr. Ebert proceeded to investigate the inductive capacity of the microsomes of the avian heart on a labile

and normally noncardiogenic tissue, the avian chorioallantoic membrane. The Rous Number 1 chicken sarcoma virus was chosen to facilitate passage of the mircosomes into cells of the membrane. The combination of the microsomes and the virus was carried out by the digestion of combined equal quantities of fresh Rous sarcoma and fresh chicken heart, followed by differential centrifugation of the mixture. The product of the centrifugation, a suspension of Rous sarcoma and heart microsomes, was used to inoculate the chorioallantoic membranes of 11-day-old chick embryos. The inoculation of Rous sarcoma and heart microsomes induced growths on the membrane. Also, inoculations of Rous sarcoma microsomes alone induced growths. In contrast, no growths were induced by the inoculations of heart microsomes alone. When the growths were sectioned and the stained sections examined, it was found that growths induced by Rous sarcoma and heart microsomes were distinctive in having developed cross-striated muscle or muscle-like elements along with the typical sarcoma cells. No such differentiations were found in the growths induced by the sarcoma microsomes alone.

The interpretation of these recent findings is awaited with much interest. Upon them will be based a significant number of the future studies on cardiogenesis. The model of cardiogenesis now being fitted together at the molecular level will also take on new meaning as a result of these findings and their meanings. One measure of the progress in any field of research is the scope of the teaching and the penetrance of new questions which the available information stimulates. It is pertinent to note in this connection that today our students repeat the observations of Aristotle at the cellular and macromolecular levels by routinely viewing the twitchings of individual fibers of heart muscle grown in tissue culture and the shortening of purified heart protein threads when adenosine triphosphate (ATP) is added to them.

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Clinical Communications

The Influence of Hereditary and Environmental Factors on the Course of Hypertensive Disease (On the Basis of Long-Term Observations of Patients)

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In a previous paper from the Institute of Therapy[1] it was shown that the hereditary factor plays a significant role in the pathogenesis of hypertensive disease (essential hypertension). At the same time, several observations showed that the hereditary factor is not fatal, and that its presence in a certain individual does not predetermine the development in him of hypertensive disease.

Various influences of the environment in which the man lives all of his life exert a great influence on his organism, and on hereditary factors. In some cases these influences promote, whereas in others they inhibit, the manifestation of hereditary factors and the development of illness.

In this paper, we present the results of observations which were made for many years on a group of patients with hypertensive disease. We tried to study the effect which the hereditary factor exerts on the course of the illness, on the one hand, and the effect which several environmental factors and the conditions under which these patients live and work exerts, on the other.

In 1952, the collaborators of the Institute of Therapy examined the workers of several factories in Moscow. The persons who were suffering from hypertensive disease were at once taken under dispensary observation. Dr. Beljaeva had a group of such persons under constant observation from 1952 till 1959, i.e., 8 years.

We must underscore the fact that the heredity of those patients was studied and recorded in their histories, but the same prophylactic and medical measures were used in *all* patients of the group, without taking into account the presence or absence of an hereditary factor. Now at the end of 8 years of observation, we have studied the results, dividing all the patients into two groups: one with the presence of the hereditary factor, and the other without it.

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There were 127 patients with hypertensive disease under observation; most of them were women. In the first group, which consisted of 94 persons, we could not establish hereditary factors concerning hypertensive disease. In the second group, which consisted of 33 persons, we found a history of hypertensive disease in the patients' parents (and in some of their other relatives also). The persons in both groups were of similar age; the majority of them were under 40 years old. In 71 patients, we found the I-B stage, and in 56 the II-A stage, of hypertensive disease.

The results of systematic dispensary observations are given in Table I.

Of the total 127 patients, we found a "recovery" in half (64). Under the term "recovery" we listed only persons in whom all the subjective and objective manifestations of hypertensive disease had disappeared, and in whom the arterial pressure had been normal for no less than 3 years. Twenty-three patients showed a marked improvement. We could not register changes in the health of 29 patients, and in 11 patients we observed an aggravation and a progression of their illness.

It should be noted that of 64 patients who "recovered," 59 were in the I-B stage of the disease, and only 5 were in the II-A stage.

TABLE I. THE RESULTS OF DISPENSARY OBSERVATIONS DURING 8 YEARS

	STAGE OF ILLNESS	NUMBER OF PATIENTS	RECOVERY	IMPROVEMENT	NO CHANGE	AGGRAVATION
Hereditary factor absent	I-B	57	47	—	7	3
	II-A	37	5	15	15	2
Total		94	52	15	22	5
Hereditary factor present	I-B	14	12	—	1	1
	II-A	19	—	8	6	5
Total		33	12	8	7	6
Grand Total		127	64	23	29	11

The results above are given for the whole group of our patients. If we analyze separately the results obtained in the two groups, we can see a marked difference between them. In the first group without the hereditary factor the best results, i.e., "recovery," were registered in 52 of 94 patients, or in more than half of all cases. Aggravation was registered in only 5 persons. In the second group with the presence of the hereditary factor, "recovery" was registered in only 12 of 33 patients, or in only one third of all cases. Aggravation was registered in 6 persons, that is, was three times more frequent than in the first group. Moreover, in the patients in the II-A stage without hereditary factor, "recovery" was registered in 5 cases. In patients in the same stage of the disease, but with the presence of an hereditary factor, such a result could not be seen in any case.

We noted that the hereditary factor plays a marked role in the course of the hypertensive disease. In the group of patients in whom it was present the application of systematic prophylactic and medical measures was less effective, and the percentage of aggravation was higher than in the group of patients without the hereditary factor.

As was said before, we applied systematically a series of prophylactic and medical measures to our patients. We prescribed a definite regimen of life and work, and controlled its fulfillment. We helped the patients to change to easier work, especially to leave nighttime work. We sent them to the night sanatoriums of the factory. We procured places for them in sanatoriums and rest homes during their annual vacations. We aided them in the improvement of their lodging conditions. The purpose of all those measures was: (1) the organization of most of the physiologic conditions of life and work, and (2) the elimination of various noxious factors in the environment.

In the majority of our patients (98) we could carry out all of the necessary prophylactic and medical measures. In the minority of patients (29) it was possible to do this only partially.

Table II gives the results obtained in these two groups. This table shows clearly how the systematic and complete application of the planned prophylactic and medical measures and the elimination of noxious environmental factors influences the course of the illness in hypertensive patients. So in 70 of the patients without an hereditary factor (the upper part of the table), we obtained much better results than in 24 similar patients in whom these measures could be realized only partially. Of the first 70 patients, "recovery" was recorded in 44, i.e., more than half. At the same time, in the second group of 24 patients, "recovery" was recorded in only 8, i.e., one third. The difference between the two groups is much more marked when we compare the poor results. From the 70 patients of the first group, "no change" was observed in 10, and "aggravation" in 3, which is a total of one fifth of all cases. At the same time, in the second group of 24 patients "no change" was registered in 12, and "aggravation" in 2, which is a little more than half of all cases.

These data show definitely that in hypertensive patients in whom the hereditary factor is absent, the fulfillment of prophylactic measures and the elimination of noxious environmental factors, in so far as possible, play a very important role —very probably, a leading role—in the course of the hypertensive disease.

The lower part of Table II shows the role of prophylactic and medical measures and the elimination of noxious environmental factors on the course of illness in hypertensive patients in whom hereditary factors are present. In the group of patients in whom proposed prophylactic measures were fully realized, we obtained "recovery" in only 12 of the 28 persons. This is not so good as in patients without an hereditary factor (44 in 70). In 5 patients in whom the hereditary factor was present, and in whom prophylactic measures could be realized only partially, an "improvement" was registered in only 1 person; in 3 others there was "no change," and in 1 we saw an "aggravation" of the disease.

These data show that in hypertensive patients in whom the hereditary factor is present the systematic and complete application of prophylactic and medical measures and the elimination of noxious environmental factors play an important role in the course of their illness. This is especially well demonstrated in the 12 patients in whom "recovery" was registered. It seems that in them the decisive role in the course of hypertensive disease was played not by the hereditary factor, but by the environmental factors.

TABLE II. THE RESULTS OF APPLICATION OF PROPHYLACTIC AND MEDICAL MEASURES

	STAGE OF ILLNESS	PROPHYLACTIC MEASURES REALIZED FULLY					PROPHYLACTIC MEASURES REALIZED PARTIALLY				
		NUMBER OF PATIENTS	RE-COVERY	IMPROVE-MENT	NO CHANGE	AGGRA-VATION	NUMBER OF PATIENTS	RE-COVERY	IMPROVE-MENT	NO CHANGE	AGGRA-VATION
Hereditary factor absent	I-B	43	39	—	3	1	14	8	–	4	2
	II-A	27	5	13	7	2	10	–	2	8	–
Total		70	44	13	10	3	24	8	2	12	2
Hereditary factor present	I-B	12	12	—	—	–	2	–	–	1	1
	II-A	16	—	7	4	5	3	–	1	2	–
Total		28	12	7	4	5	5	–	1	3	1
Grand Total		98	56	20	14	8	29	8	3	15	3

In the course of the treatment, we tried to establish which environmental factors present in each case could produce an unfavorable effect on the course of the hypertensive disease. In the majority of cases it was possible to find among several factors the principal or leading one. Without elimination of this dominant factor, all prophylactic and medical measures had only a temporary effect or no effect at all. For instance, night work was, as a rule, a heavy burden to patients with hypertensive disease. Strongly positive results from our measures were obtained only after our patients were transferred from night shifts to day shifts. In the upper part of Table III, one can see that in 18 such patients, recovery was observed in 14. The elimination of the noxious factor of work on the night shifts gave good results not only in patients without an hereditary factor, but also in those with an hereditary factor.

Table III

	NUMBER OF PATIENTS	RECOVERY	IMPROVEMENT	NO CHANGE	AGGRAVATION	
Release From Night Work						
Hereditary factor absent	13	11	1*	—	1	* II-A stage of hypertensive disease
Hereditary factor present	5	3	—	1*	1*	
Total	18	14	1	1	2	
Improvement of Living Conditions						
Hereditary factor absent	8	7	—	—	1	* II-A stage of hypertensive disease
Hereditary factor present	5	3	1*	1	—	
Total	13	10	1*	1	1	

In another group of our patients, we could establish the prominent noxious role played by their living and domestic conditions. The majority of these persons lived in the suburbs and were obliged to spend 3 to 4 hours daily traveling to and from their homes. In other patients who lived in town, we found other harmful factors connected with their housing and family conditions. We tried to eliminate these noxious factors in 13 patients of this group. The inhabitants of the suburbs were lodged in town so that they did not need to make long daily trips. Others received new separate lodgings, which excluded domestic familial conflicts. The lower part of Table III shows that of the group of 13 such patients the effect was very good in 10, and "recovery" was registered. Such positive results were obtained not only by patients without an hereditary factor, but also by those with an hereditary factor.

A few illustrations will show the influence of noxious environmental factors and their elimination on the course of hypertensive disease.

Case 1.—S. was a 27-year-old woman in whom the hereditary factor was absent. Her hypertensive disease was of the I-B stage. In 1952, and the first half of 1953, the blood pressure was 165/115-155/100 mm. Hg. The patient lived with her aunt, and they quarreled frequently. In the second

half of 1953, the patient lived nearly all of the time in the night sanatorium of the factory. The blood pressure at this time became normal, but rose at once when the patient returned home (160/100 mm. Hg). The patient was advised and helped to leave her aunt and to live separately, and at the end of 1954, the blood pressure dropped to 130/90 mm. Hg. The next year the blood pressure became normal (120/80 mm. Hg), and from 1955 until 1960 has remained normal (Fig. 1).

Case 2.—B. was a 34-year-old woman with hypertensive disease of the I-B stage. Her mother and two sisters suffered from hypertensive disease. The patient lived with her husband and his family and had very frequent arguments with the members of that family. In the years 1953-1956, the blood pressure was elevated and reached 170/90-165/100 mm. Hg. She was placed in the night sanatorium of the factory three times, and each time the blood pressure became normal. In 1956, she and her husband left his family and now live separately. The blood pressure of the patient dropped to 130/85 mm. Hg. In 1957, 1958, and 1959, the blood pressure was always found to be normal (Fig. 2).

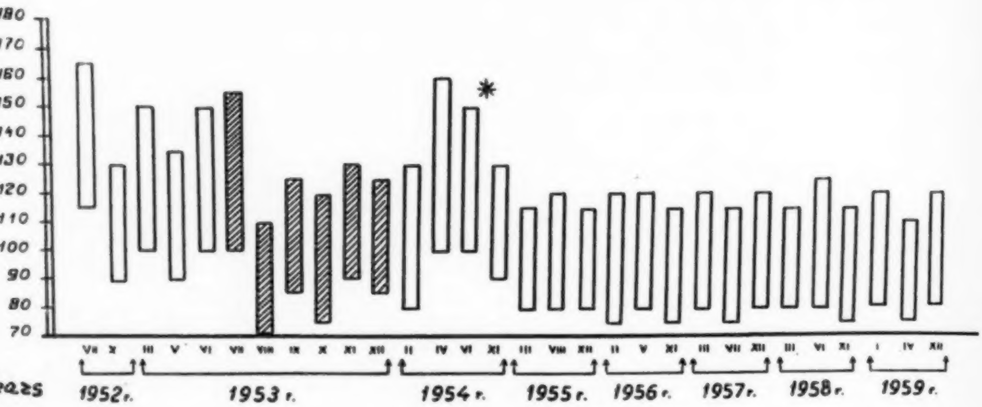

Fig. 1.—Case 1. The shaded columns give the blood pressure of the patient when she was in the night sanatorium. The asterisk marks the time when the patient left her aunt.

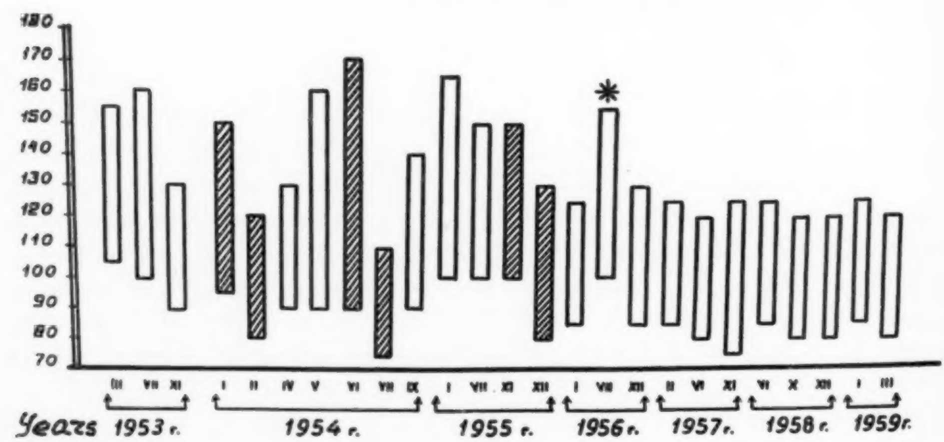

Fig. 2.—Case 2. The shaded columns give the blood pressure of the patient when she was in the night sanatorium. The asterisk marks the time when the patient and her husband left his family.

Both examples prove the great influence of noxious environmental factors and of their elimination. In the second case, environmental factors were clearly more important than hereditary factors. Identical illustrations could be given for the role of a change from night work to day work. The environmental factors which

play an important role in the course of hypertensive disease can be very different in different persons. In many cases these factors are very spectacular, and can be easily found and appreciated. But in other cases their detection is not easy. The patients are not aware of them, or sometimes they do not want to speak of them to the doctor. Case 3 represents such an example.

CASE 3.—M. was a 25-year-old girl in whom there was no hereditary factor. The hypertensive disease was of the II-A stage. In the years 1953, 1954, 1955, and the first half of 1956, the blood pressure was found to be elevated, and rose as high as 180/120 mm. Hg. Twice when she was staying in the night sanatorium of the factory, the blood pressure became normal, but quickly rose again. Several talks in search of factors which might be causing the hypertony were unsuccessful. The patient was hospitalized in the clinic of the Institute of Therapy, but there also nothing pertinent could be found, and the patient was dismissed. In the middle of 1956, the girl married, and the marriage was happy. The blood pressure gradually dropped, became normal, and remained normal during 1957, 1958, and 1959 (Fig. 3). We think that our patient had a feeling of dissatisfaction in her personal life. Perhaps she was not conscious of the cause, could not exactly express it, or was too shy to speak about it to the doctor. Only the successful solution of the question, the happy marriage, led to a major change in the course of her hypertensive disease.

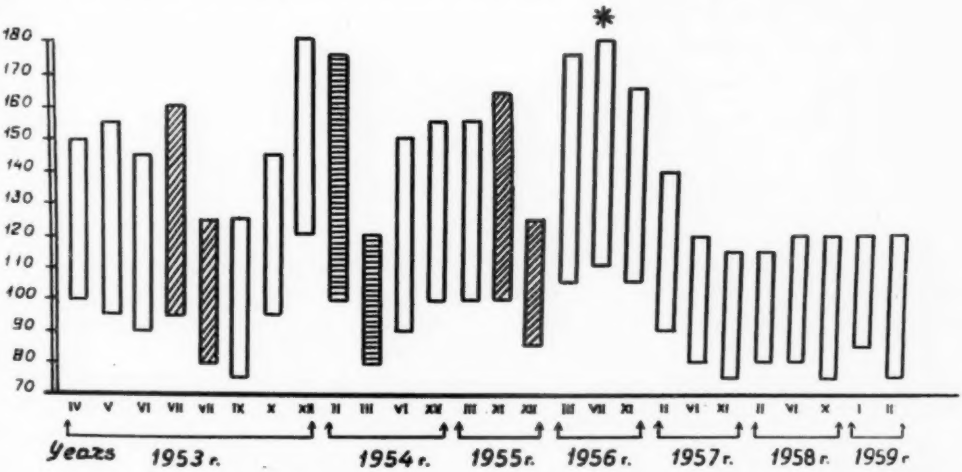

Fig. 3.—Case 3. The shaded columns give the blood pressure of the patient when she was in the night sanatorium and the clinic. The asterisk marks the time of her marriage.

CONCLUSIONS

1. The hereditary factor plays a definite role in the course of hypertensive disease, in the sense that in hereditarily tainted persons the results of prophylactic and medical measures are less effective. The percentage of "recoveries" is smaller, and the number of the cases with aggravation and progression of the illness is higher.

2. However, in hereditarily tainted patients, systematic application of prophylactic and medical measures and elimination of various noxious environmental factors is of great importance, and often has a decisive influence on the course of the hypertensive disease.

3. The results of prophylactic and medical measures and the elimination of noxious environmental factors are more effective when begun in the first stages of the illness.

4. In hypertensive disease the hereditary factor is not fatal, and its influence can be neutralized by early and systematic application of the necessary prophylactic and medical measures.

REFERENCE

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Bacteremia Following Sigmoidoscopy

Elwood Buchman, M.D., and Earl M. Berglund, B.S.,** Iowa City, Iowa*

Bacteremia is known to follow dental extractions, many surgical procedures, and irritation of foci of infection.[1-23] An excellent review of the bacteremia which follows instrumentation has been written by Nissen.[19] In a preliminary study by Unterman and associates,[21] in only one instance in a series of 50 patients was a case of bacteremia found that may have been induced by sigmoidoscopy. Our interest was to explore further the possibility of sigmoidoscopy leading to transient bacteremia. If such a case of bacteremia truly occurred, there would be an excellent basis for antibiotic prophylaxis in an effort to prevent bacterial endocarditis in patients with valvular heart disease.

METHOD

A sigmoidoscopic examination was performed on 100 patients who were on the Medical Service for the usual indication of the procedure. Patients who were, or had been, on antibacterial drugs within 2 weeks of sigmoidoscopy were excluded from the study. The sigmoidoscope was inserted its full length (25 centimeters or 10 inches) or nearly so in all patients.

The antecubital areas of the patients' arms were vigorously prepared with a cotton sponge saturated with 70 per cent alcohol. Approximately 5 ml. of blood were aspirated from the antecubital veins and aseptically deposited in 60 ml. of heart-infusion broth which contained traces of cystine and p-aminobenzoic acid and 0.1 per cent agar. The cultures were incubated at 37.5°C. in a 10 per cent atmosphere of carbon dioxide. They were examined daily for a period of 10 days, at the end of which time they were reported to be negative if no growth had appeared. Cultures with growth were transferred to appropriate media for definitive identification of organisms.

The specimens of blood were collected from each arm immediately before, immediately after, and 15 minutes after sigmoidoscopy.

RESULTS

In 87 of the 100 patients, blood cultures from both arms were negative before, immediately after, and 15 minutes after sigmoidoscopy. Blood cultures in 13 additional patients showed no growth in blood taken from one arm, but

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organisms were cultured in a single specimen taken from the other arm. Thus, of the 600 blood cultures which were obtained, growth occurred in only 13 instances. These findings are tabulated in Table I. No patient whose stool was cultured showed evidence of enteric pathogens.

TABLE I. RESULTS OF BLOOD CULTURES IN 100 SIGMOIDOSCOPIC EXAMINATIONS

NUMBER OF PATIENTS	SOURCE OF SPECIMENS OF BLOOD	BEFORE SIGMOIDOSCOPY	IMMEDIATELY AFTER SIGMOIDOSCOPY	15 MINUTES AFTER SIGMOIDOSCOPY
87	Both arms	No growth	No growth	No growth
13	One arm	No growth	No growth	No growth
4	One arm	No growth	Hemolytic Staphylococcus (coagulase negative)	No growth
1	One arm	No growth	Species of bacillus	No growth
1	One arm	Nonhemolytic Staphylococcus (coagulase negative)	No growth	No growth
4	One arm	No growth	No growth	Hemolytic Staphylococcus (coagulase negative)
1	One arm	No growth	No growth	Species of Corynebacterium
1	One arm	No growth	No growth	Species of anaerobic Corynebacterium
1	One arm	No growth	No growth	Hemolytic Staphylococcus epidermidis (coagulase negative)

DISCUSSION

The majority of the patients in this study were found to have normal mucosa, whereas 11 patients had chronic ulcerative colitis in various stages of activity. Four patients had polyps, which were excised in 2 of the patients; and 1 patient had a polypoid adenocarcinoma of the rectum which was biopsied. Five individuals were found to have hemorrhoids, and 2 had fistulas. One patient had an anal fissure. Evidence of minor trauma was found in 4 patients; this was probably due to the manipulation of the sigmoidoscope or enema tip.

In only 5 patients did blood cultures grow bacteria immediately after sigmoidoscopy. Two of these isolates were coagulase-negative staphylococci, and one isolate was a species of bacillus. Thus, it is believed that bacteremia was not induced by sigmoidoscopy.

It is of interest that in patients in whom positive blood cultures were obtained, the mucosa at the time of sigmoidoscopy appeared to be entirely normal, without visibly active lesions.

The apparent infrequency of bacteremia after sigmoidoscopy has been postulated to be due to high resistance of rectal mucosa to bacterial invasion and/or prompt removal of bacteria from the portal circulation by the reticuloendothelial system of the liver.[19,22,23] The inability to recover organisms from samples of blood in this study may be due to several conditions. One likely possibility is that no bacteremia existed at all. However, the clearing of the blood stream by

defense mechanisms of the body should also be considered. Although the cultural environment outlined for this study would seem to be suitable for the organism requirements of the expected flora, it is possible that the proper conditions may not have been provided.

It would seem that antibiotic prophylactic treatment is not necessary in the presence of cardiac abnormalities (valvular or endocardial) prior to the procedure of sigmoidoscopy.

SUMMARY AND CONCLUSIONS

Sigmoidoscopy was evaluated as a possible cause of transient bacteremia in 100 patients who had not been on antibacterial drugs in the immediate preinstrumentation period. Specimens of blood were taken for bacterial culture before, immediately after, and 15 minutes after sigmoidoscopy. Samples of blood were taken from each arm in order to facilitate a check against contamination.

In 87 patients, blood cultures were negative after sigmoidoscopy. Bacteria were recovered from only 1 of the 200 presigmoidoscopy specimens of blood, and from only 12 of the 400 cultures obtained after sigmoidoscopy. In no instance was the organism recovered from blood drawn simultaneously from each arm. Most, if not all, of the positive cultures are believed to have been chance contaminants. Bacteria infrequently followed sigmoidoscopy.

The authors wish to express gratitude to Doris M. Jones, R.N., who kindly assisted with the sigmoidoscopies and venipunctures.

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The Response of the Serum Glutamic Oxalacetic Transaminase to Open-Heart Operation

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INTRODUCTION

In spite of the wide interest that the determination of serum glutamic oxalacetic transaminase (SGOT) has attracted in many areas of medicine since the original report of La Due and associates,[1] only a few publications have appeared pertaining to the effects of operations, and of cardiovascular operations in particular. Nickell and Allbritten[2] found a rough correlation between the degree of surgical trauma and the elevation of the level of SGOT. Thoracotomies produced a more pronounced rise than did laparotomies, with the exception of gall-bladder operations. Craver and associates[3] have come to the same conclusion. The latter authors did not find a return to normal values before the fourth postoperative day. Person and Judge,[4] on the other hand, could not demonstrate a significant rise in SGOT in 46 surgical patients, except under the following conditions: (1) liver biopsies and subphrenic abscesses; (2) biliary tract operation; (3) extensive skeletal muscle trauma; (4) postoperative complications with hematomas or hemolysis; (5) pulmonary resection; (6) elevated preoperative levels; (7) possibly prolonged anesthesia. Picktin and associates[5] showed a rise in the level of SGOT which corresponded to the extent of injury to tissue in patients with extensive burns. Lawrence and Schulkins[6] were unable to find that the type of anesthesia employed had any influence on the postoperative elevation of SGOT. They also found higher elevations after thoracotomies than after laparotomies. Di Carlo and associates[7] stress the fact that the amount of muscular damage is of paramount importance; in their series of 70 patients, those who had had radical mastectomies and the amputation of limbs showed the highest values. Candura and Minardi[8] could not demonstrate significant elevations, except after cholecystectomy.

Reports are even more sparse in regard to cardiovascular operations. To our knowledge, there are only three reports in the literature at the present time.

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Von Schlief and Kamm[9,10] have studied pulmonary valvulotomies by the transventricular approach, mitral valvulotomies, and ligation of patent ductus, and found the highest values in the first group, smaller values in the second group, and only insignificant elevations in the latter group.

Snyder and associates,[11] who evaluated 28 patients undergoing total body perfusion, demonstrated elevations in SGOT that they considered to be related to the degree of cardiac muscle trauma. Thus, the highest levels of SGOT were noted in patients with tetralogy of Fallot; next in order were those in patients with ventricular septal defect, and the smallest elevations were found in patients undergoing perfusion without ventriculotomy.

These few studies on the effect of cardiovascular operations on the level of SGOT would tend to indicate that many questions remain unanswered, and it seemed justified to seek further information on this subject.

METHOD

Forty-eight patients who were undergoing a variety of cardiovascular operations were studied. The method described by Karmen and associates was used in the analysis of the SGOT values.[12] The values were determined 1 day preoperatively, 6 hours postoperatively, and on the first, second, and third postoperative days.

Patients 1-27 were operated upon under conditions of cardiopulmonary bypass with a modified Kay-Cross pump with disc oxygenator and hypothermia, if not indicated otherwise in Tables I-IV. Coronary perfusion was not employed.

In Patients 34-44, hypothermia and circulatory occlusion were used in addition to general anesthesia. The remainder of the patients were operated upon under general anesthesia alone.

Samples of blood were either processed immediately, or the plasma was separated and stored at 0°C. Hemolyzed samples which contained more than 80 to 100 mg. of free hemoglobin—this degree of hemolysis can easily be detected macroscopically—were eliminated, although our own experiments have shown that this extent of hemolysis does not significantly alter the SGOT values.

RESULTS

As may be seen from Figs. 1-3, there is great variation in the magnitude of the elevation of the level of SGOT in patients undergoing open-heart procedures under conditions of cardiopulmonary bypass.

Statistical analysis shows that there are no significant differences in the three groups into which we have subdivided our patients: namely, (1) tetralogy of Fallot; (2) ventricular septal defect approached via the ventricle; (3) ventricular septal defect and atrioventricularis communis defect approached via the auricle.

There is, however, a significant difference between these three groups and others in which intracardiac procedures were performed without the aid of extracorporeal circulation: namely, atrial septal defects repaired under hypothermia and general anesthesia; and mitral commissurotomies, patent ductus, and coarctations of the aorta, under general anesthesia alone or with hypothermia in addition.

It is readily noted from the figures that the SGOT reached much higher values in patients who expired in the immediate postoperative period (Patients 3, 8, 14, 19, 22, 23, 26) than in those patients who survived. A 4-year-old girl

with a ventricular septal defect which was repaired by the ventricular approach was the only patient with a peak elevation of over 300 units who survived the surgical procedure (Patient 13).

In contrast to the afore-mentioned patient with the high level of SGOT, in whom the operative procedure and postoperative course were uncomplicated, Patient 20 is of interest. Patient 20, with a tetralogy of Fallot, had a peak value of only 148 units, despite a complicated course which included cardiac standstill on several occasions, necessitating cardiac massage, removal of infundibular tissue, and insertion of plastic material into the ventricular septal defect and outflow tract of the right ventricle.

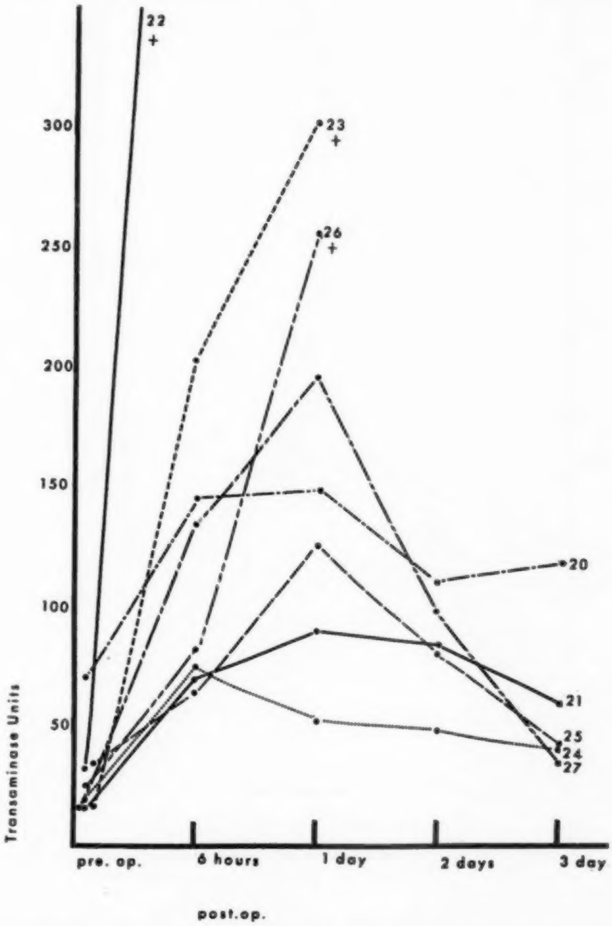

Fig. 1.—Pre- and postoperative levels of SGOT in 8 patients undergoing correction of tetralogy of Fallot under conditions of cardiopulmonary bypass (+ = patient expired).

Patient 31 was also of interest in that she had infectious hepatitis 3 months prior to operation and an elevation of total bilirubin to 3.5 mg. per cent postoperatively, which was attributed to the liver disease; the peak postoperative transaminase value, however, was only 57 units.

In the group of patients who were operated upon without the use of extracorporeal circulation, the highest value observed was 288 units 6 hours post-

operatively in a 6-year-old girl in whom, during a previous operation, the inferior vena cava had been inadvertently transposed. This patient died 12 hours postoperatively as a result of massive hemorrhage (Patient 40). Only 2 patients in this group (Patients 28 and 35), one who underwent mitral commissurotomy, and the other who underwent closure of an atrial septal defect, had a rise in SGOT values above 100 units.

Autopsies were performed on 4 of the patients who expired in the immediate postoperative period. These patients did not reveal acute necrosis of either liver or myocardium.

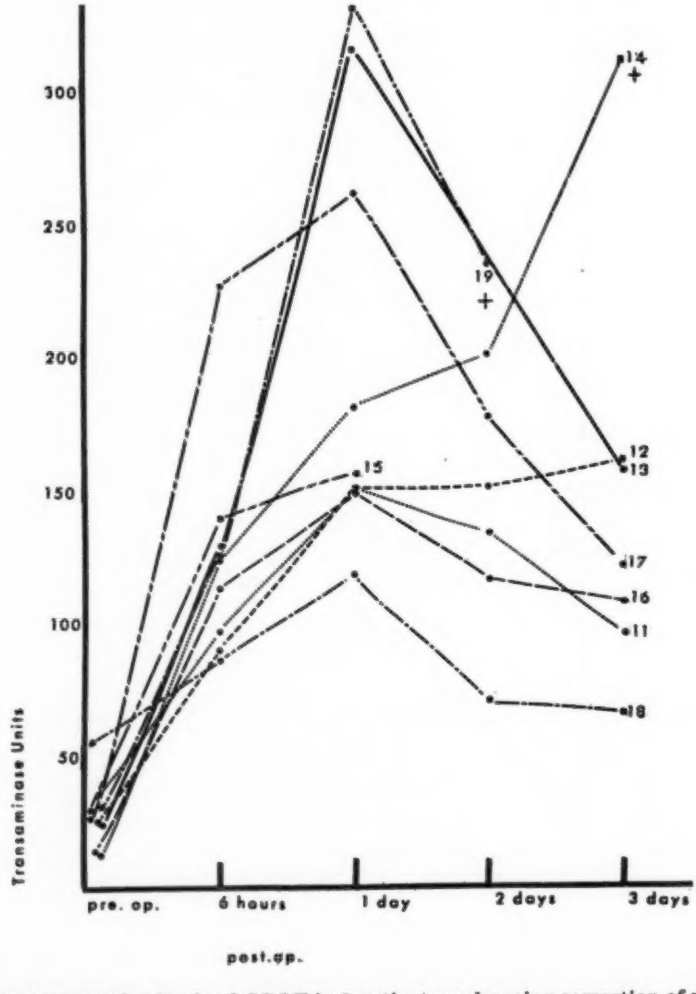

Fig. 2.—Pre- and postoperative levels of SGOT in 9 patients undergoing correction of ventricular septal defect by the ventricular approach under conditions of cardiopulmonary bypass (+ = patient expired).

DISCUSSION

A review of the results of this study would not appear to indicate any obvious relationship between the degree of the mechanical trauma to the myocardium during operation and the extent of the elevation of the level of SGOT in the postoperative period. Neither could we detect a positive relationship between

the duration of circulatory occlusion and the postoperative level of SGOT in those patients with atrial septal defects who were operated upon under conditions of hypothermia. Nor was there a positive relationship between the postoperative level of enzyme and the perfusion rate in patients operated upon under conditions of cardiopulmonary bypass.

There was, however, a distinct difference between those patients operated upon under cardiopulmonary bypass who expired in the immediate postoperative period and those who survived. The difference in the peak postoperative values between the group operated upon under cardiopulmonary bypass and the group

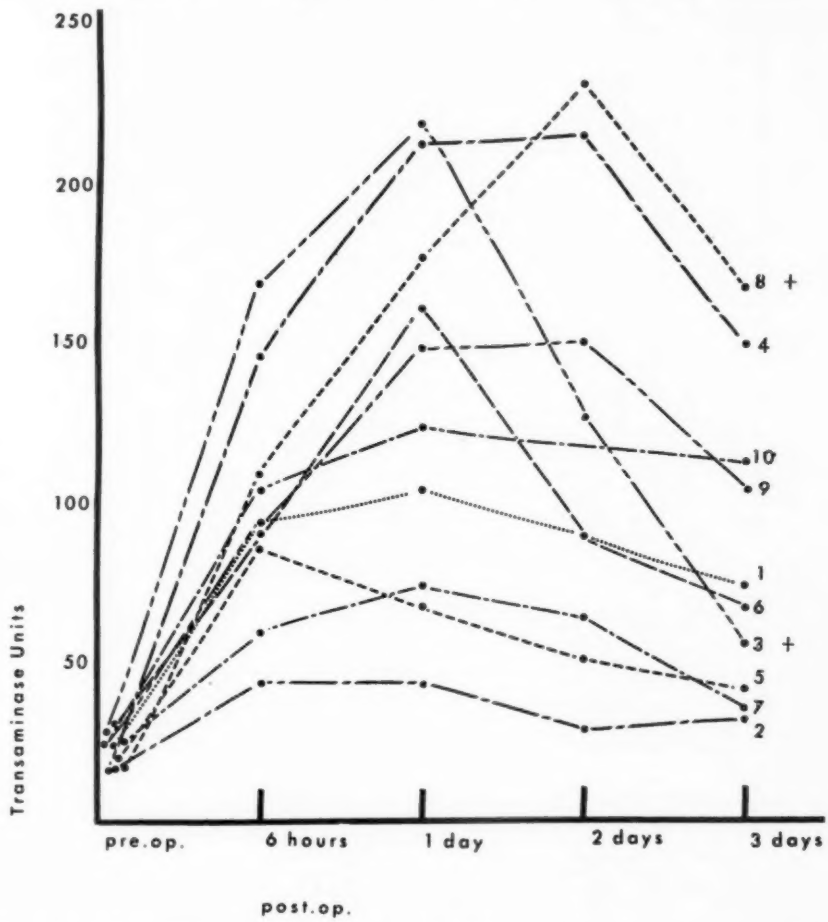

Fig. 3.—Pre- and postoperative levels of SGOT in 10 patients undergoing correction of ventricular septal defect or atrioventricularis communis defect by the auricular approach under conditions of cardiopulmonary bypass (+ = patient expired).

operated upon under general anesthesia and/or hypothermia was also significant (20 patients in each group; average peak value, 145 versus 74 units). There was also a positive correlation between the duration of cardiopulmonary bypass and the level of the postoperative SGOT values (an average of 363 units with cardiopulmonary bypass of more than 40 minutes, compared with an average of 118 units when bypass time was less than 40 minutes).

TABLE I. VENTRICULAR SEPTAL DEFECT AND A-V COMMUNIS DEFECT UNDER CIRCULATORY BYPASS AND HYPOTHERMIA. AURICULOTOMY ONLY

PATIENT	DIAGNOSIS	PUMP TIME (MIN.)	SGOT LEVELS					REMARKS
				POSTOP.				
			PREOP.	6 HR.	FIRST DAY	SECOND DAY	THIRD DAY	
1. J. C.	VSD	28	24	93	103	89	73	Clinically, defect seems to be still open. NSR postop.
2. D. P.	A-V communis	32	17	43	43	28	31	Uncomplicated postop. course
3. C. L.	A-V communis	98	28	168	218	126	55	3° block postop., pulmonary edema, renal shut-down; expired fourth day postop.
4. R. K.	A-V communis; PDA	27	16	145	212	214	148	Short run of ventricular fibrillation at operation. RBBB postop.
5. P. J.	VSD; pulmonary hypertension	30	20	85	67	50	41	A-V dissociation postop.
6. R. R.	A-V communis	35	31	89	160	88	66	Ventricular fibrillation at operation. Electroshock
7. B. K.	A-V communis	34	26	58	73	63	34	Patch inserted, auricular flutter and RBBB postop. for several days; expired twentieth day postop., pneumonia
8. V. L.	A-V communis	54	23	108	176	231	166	15 min. ventricular fibrillation; postop. brain damage by EEG; expired fifth day; no autopsy
9. J. W.	ASD primum	48	23	94	148	149	103	Occasional atrial tachycardia postop. SBE postop.
10. L. H.	ASD primum	21	24	103	123	—	112	Short ventricular fibrillation at operation, massage

Table II. Ventricular Septal Defect Under Circulatory Bypass and Hypothermia. Ventriculotomy

PATIENT	DIAGNOSIS	PUMP TIME (MIN.)	SGOT LEVELS					REMARKS
			PREOP.	POSTOP.				
				6 HR.	FIRST DAY	SECOND DAY	THIRD DAY	
11. P. J.	VSD	37	35	96	150	133	95	20 min. ventricular fibrillation at operation, massage
12. J. R.	VSD	32	25	89	150	150	160	Ventricular fibrillation at operation, massage, shock, defect not closed, iatrogenic AI
13. G. L.	VSD	10	24	128	315	—	156	No hypothermia, ventricular fibrillation at operation, massage
14. F. Ch.	VSD	26	13	123	180	200	310	5 min. ventricular fibrillation at operation, massage, nodal tachycardia postop. 3° block, PH; expired fourth day postop.
15. V. A.	VSD	30	29	139	155	—	—	No hypothermia, infarct (?) by ECG, RBBB postop.
16. G. W.	VSD; AI	45	14	112	149	115	106	AI not repaired. RBBB postop., 25 min. ventricular fibrillation at operation, massage, shock
17. A. A.	VSD; PDA	20	26	226	261	176	120	20 min. massage at operation; arrest postop., massage
18. R. R.	VSD	15	54	85	119	70	65	Uncomplicated. Patch inserted. PDA ligated
19. C. M.	VSD	22	31	124	330	234	—	3° block, frequent asystole; expired third day postop.

TABLE III. TETRALOGY OF FALLOT UNDER CIRCULATORY BYPASS

PATIENT	DIAGNOSIS	PUMP TIME (MIN.)	SGOT LEVELS					REMARKS
			PREOP.	POSTOP.				
				6 HR.	FIRST DAY	SECOND DAY	THIRD DAY	
20. J. G.	Tetralogy	27	70	141	148	110	118	Cardiac arrest during cooling, massage, prosthetic closure of defect, patch in outflow tract, RBBB postop.
21. W. H.	Tetralogy	30	14	69	89	84	59	RBBB postop.
22. D. S.	Tetralogy	68	33	1,180	—	—	—	Cardiac arrest during cooling, prosthesis in defect and outflow tract. 20 min. ventricular fibrillation at operation; expired 6 hr. postop.
23. R. H.	Tetralogy	63	16	203	302	—	—	Patch inserted in VSD. Patch in outflow tract. RBBB postop. Expired 36 hr. postop. in circulatory failure
24. N. McD.	Tetralogy	40	18	74	52	48	40	Patch in VSD, RBBB postop.
25. P. L.	Tetralogy	39	34	63	125	80	42	Patch in VSD, RBBB postop.
26. M. M.	Functional single ventricle	90	25	82	266	—	—	2 patches in VSD, 1 patch in outflow tract. 25 min. at operation, 3° block. Expired 26 hr. postop. in circulatory failure
27. R. W.	Tetralogy	85	16	134	195	98	34	1 patch in defect, 1 patch in outflow tract. RBBB, probably aneurysm of outflow tract

TABLE IV. MISCELLANEOUS OPERATIONS WITHOUT CARDIOPULMONARY BYPASS

PATIENT	DIAGNOSIS	ANESTHESIA	OCCLUSION TIME	SGOT LEVELS					REMARKS
					POSTOP.				
				PREOP.	6 HR.	FIRST DAY	SECOND DAY	THIRD DAY	
28. H. S.	MS	General	—	25	57	142	69	55	Second operation because of re-stenosis. AF
29. G. S.	MS	General	—	11	21	45	39	28	Wound infection
30. A. G.	MS	General	—	9	31	41	27	17	Expired 3 mo. postop. cardiac arrest; no autopsy
31. B. M.	MS	General	—	36	57	57	54	37	Hepatitis 3 mo. preop., AF Total bilirubin 3.5 mg. 5 days postop.
32. J. R.	MS	General	—	19	—	92	63	49	—
33. B. S.	MS	General	—	22	69	79	52	69	—
34. D. T.	ASD, secundum	General; hypothermia	4′5″	19	67	74	37	31	—
35. J. B.	ASD	General	5′ 20″	17	140	—	76	65	Auricular flutter preop., RSR postop.
36. D. K.	ASD	General	7′ 35″	11	83	84	81	70	—
37. T. P.	ASD	General	7′	18	47	64	43	32	—
38. S. P.	ASD	General	5′ 45″	25	61	83	81	49	—
39. S. L.	ASD	General	4′ 55″	15	42	61	30	31	Auricular flutter with ventricular rate of 280 at operation
40. B. B.	Transposition of IVC	General	13′ 55″	19	288	—	—	—	Iatrogenic transposition of IVC on previous operation, 4 occlusions; expired 12 hr. postop., massive bleeding
41. L. N.	ASD, secundum	General	7′ 30″	17	79	75	69	63	2 occlusions
42. G. C.	ASD	General	3′ 30″	29	76	81	35	—	—
43. L. N.	Sinus of Valsalva aneurysm	General	5′ 50″	27	86	94	85	52	2 occlusions
44. E. S.	Trilogy	General	7′	24	49	35	29	28	—
45. D. P.	PDA	General; hypothermia	—	28	39	52	—	46	—
46. J. C.	Coarctation	General	—	32	49	59	29	20	—
47. J. B.	PDA	General	—	7	41	29	16	20	—
48. W. C.	Coarctation	General; hypothermia	—	15	23	63	56	56	—

These results are only partly in agreement with those of Snyder and associates,[11] who have reported on a similar study and found significant differences between patients with tetralogy of Fallot and those with ventricular septal defects, both operated upon under conditions of cardiopulmonary bypass. The average values in their patients were higher than those in this series. We agree, however, with them that the myocardium is but one source from which SGOT may be liberated. The histologic studies of the liver in patients who succumbed to operation did not show extensive centrilobular necrosis, which has recently been suggested as being the source of elevated SGOT in patients in whom acute heart failure is superimposed on chronic failure.[13] The chemical changes, however, may well precede the anatomic evidence, so that this fact, in our opinion, does not necessarily militate against the possible contributing role of the liver. The effect of opiates is also not clearly understood as yet.[14]

Until recently it had been assumed that the elevation of several enzymes in the serum after myocardial infarction—and particularly glutamic oxalacetic transaminase—was produced by release of the enzymes from necrotic cells. This assumption was based on the fact that the enzymatic content of necrotic cells in a myocardial infarct fell concomitantly with the rise in the content of enzymes in the serum, and a rough correlation between the level of SGOT in the blood and the extent of the infarct was apparent.[15] Recently, however, Hauss[16,17] has advanced the concept of the "acute syndrome," and stated that the elevation of transaminase cannot be attributed solely to a local factor, but rather that it is a complex response of the whole organism. He supports this thesis by calling attention to the fact that the elevation of several enzymes in the blood serum after a myocardial infarction is also accompanied by changes in other physiologic indices, namely, azotemia, rise in blood sugar, and elevation of the sedimentation rate, which cannot wholly be attributed to the local necrosis in the heart muscle. He further supports this concept with the fact that the enzyme values determined are out of proportion to the total enzyme content of the heart muscle. He has also produced significant elevations in SGOT in rabbits by experimentally induced orthostatic collapse. Finally, there is a decrease in the level in the blood of at least one enzyme after myocardial infarction, namely, cholinesterase.

The previously mentioned fact that a simple thoracotomy elevates the level of SGOT more than do simple surgical procedures in the abdominal cavity is not in opposition to this, because the over-all influence of thoracotomy on the physiology of the whole organism may well exceed that of other procedures. Andres,[18] in a series of 43 patients who underwent a variety of surgical procedures, has also come to the conclusion that the observed elevation of SGOT is the result of the ensuing state of shock, and that the actual damage to tissue is not wholly responsible.

In our series, there was a marked difference between the peak elevation in patients perfused more than 40 minutes and the peak elevation of those perfused less than 40 minutes: namely, 363 units versus 118 units. This we do not believe can be satisfactorily explained solely by the difference in the magnitude of actual muscle damage. The same is true for the patients who did not survive the immediate postoperative period and showed a significantly higher rise in the

level of SGOT, with approximately the same amount of tissue damage. Thus, it may well be that the actual muscle damage is only one source, and probably not the most important, for the elevation of levels of serum SGOT after heart operations.

SUMMARY

In 48 patients who underwent cardiac and cardiovascular operations, the levels of SGOT were studied in the postoperative period.

There was a significant difference between a group of 27 patients who underwent intracardiac procedures with the aid of circulatory bypass and 16 patients who underwent procedures without circulatory bypass.

Within the first group—subdivided into three classes, namely, tetralogy of Fallot, ventriculotomy alone, auriculotomy alone—no significant differences were found.

Patients who did not survive the immediate postoperative period showed significantly higher values than did the survivors.

The length of the period of extracorporeal circulation correlated with the rise in the levels of SGOT, as well as with the death rate.

From these results it is concluded that the levels of SGOT—and probably levels of enzymes in general—cannot be considered as an index of tissue damage alone in patients who have undergone cardiac operation, but rather as part of a complex response of the whole organism.

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Transseptal Catheterization of the Left Heart: Observations in 56 Patients

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Right heart catheterization has been an accepted diagnostic procedure for many years for the evaluation of patients with congenital and acquired heart disease.[1-4] The data obtained from right heart catheterization are often incomplete and indirect in patients with acquired heart disease, since the lesions usually involve the mitral and aortic valves. The determination of cardiac output and the recording of pressures in the pulmonary wedge position provide restricted information pertinent to the left heart. The development of corrective operative techniques and the ready accessibility of the mitral and aortic valves have provided the proper incentive for obtaining the appropriate data from the left atrium and ventricle.

Several approaches to the left heart have been employed, and these include direct cardiac puncture by percutaneous needle from the posterior thorax,[5,6] the suprasternal notch,[7] or the anterior thorax.[8] Direct puncture through the left main-stem bronchus during bronchoscopy has been frequently employed.[9] The retrograde passage of a catheter through a peripheral artery has until recently had limited use.[10] All such approaches to the left heart involve some hazard, and the decision to utilize them has been tempered by the morbidity.[11,12] In 1958, a new approach to the left heart was developed in the cardiovascular laboratories of The National Institute of Health.[13,14] This method, termed "transseptal catheterization," involves puncturing the interatrial septum through a catheter inserted into the right atrium via a saphenous vessel. Through this needle, small plastic catheters can be introduced to explore the left heart. This method greatly simplifies catheterization of the left atrium and obviates many of the difficulties inherent in other techniques.

The purpose of the present report is to present our experience with transseptal catheterization of the left atrium in 56 patients with cardiac disease.

METHOD

The method used in our laboratory is similar to that reported by Ross.[13] The patient is given a barbiturate for its sedative effect and brought to the cardiovascular laboratory in a fasting state. Through a small transverse incision, 3 to 4 cm. below the right inguinal ligament and just medial

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to the pulsation of the femoral artery, the superficial saphenous vein is located and isolated. A No. 9, 61 cm. shortened Cournand catheter is introduced into the isolated vein and advanced under fluoroscopic control into the right atrium (Fig. 1). A No. 18, 65 cm. thin-walled needle is carefully introduced within the lumen of the catheter until its tip lies just proximal to the end of the catheter. A flexible connector between the needle and the pressure transducer allows the continuous recording of pressures in order to confirm the position of the needle tip.

Under fluoroscopic control, the catheter is directed medially and posteriorly just above the tricuspid valve into contact with the interatrial septum. Constant pressure recording is necessary, since the catheter tip may enter the right ventricle. An indicator on the hub of the catheter guides the operator in directing the needle. The needle is then advanced beyond the catheter and through the atrial septum into the left atrium. With experience, the operator detects a definite "puncture" sensation as the needle pierces the septum. A sample of left atrial blood may be withdrawn via an appropriate stopcock arrangement. Through the No. 18 needle, an 85 to 90 cm. filament catheter (size Pe-50 polyethylene) is introduced into the left atrium and advanced during constant pressure monitoring. Several attempts are then made to introduce the catheter through the mitral valve into the left ventricle. Once the left ventricle has been entered, the flow of blood will usually transport the catheter tip through the aortic valve. Withdrawal of the catheter while pressures are recorded permits an accurate determination of pressures in the aorta, left ventricle, and left atrium (Fig. 2). To terminate the procedure, the filament catheter is removed first, then the needle, and, finally, the Cournand catheter.

After the withdrawal of the No. 9 Cournand catheter, a suitable standard right heart catheter may be introduced into the same vein, and a routine right heart procedure may be carried out, with one incision serving for both procedures. If only left atrial data are required, or if the saphenous vein will only accommodate a No. 8 Cournand catheter, a No. 19 needle may be introduced for the septal puncture. However, the lumen of a No. 19 needle with standard internal caliber has not allowed passage of a plastic catheter of sufficient size to permit accurate pressure recording.

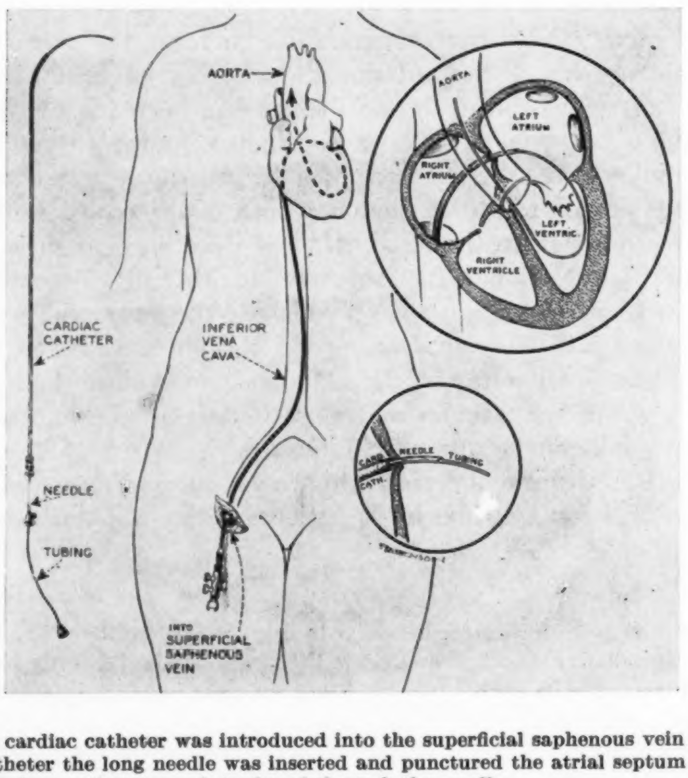

Fig. 1.—The cardiac catheter was introduced into the superficial saphenous vein of the right leg. Through this catheter the long needle was inserted and punctured the atrial septum as shown in the inset. The polyethylene catheter was introduced through the needle.

During the transseptal procedure, a routine right heart catheterization may be performed through an appropriate arm vein, so that simultaneous data may be obtained.

RESULTS

Fifty-six transseptal catheterizations have been performed in our laboratory. Entry into the left ventricle was not attempted in the patients examined initially. In 42 attempts we were successful in entering the left ventricle in 30, or 71 per cent. The aorta was entered in five cases. Only rarely was an attempt made to manipulate the catheter into the aorta after entrance had been made into the left ventricle, since, in each patient, peripheral systemic pressures were recorded from an indwelling arterial needle (Fig. 2).

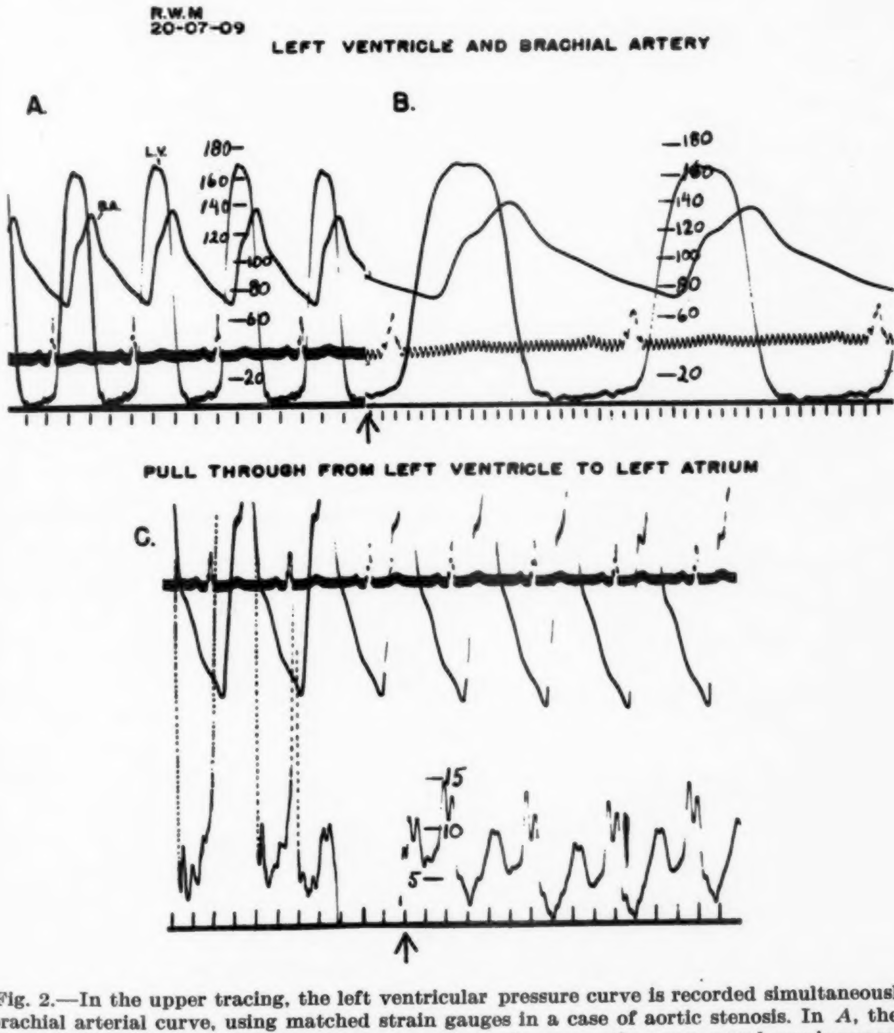

Fig. 2.—In the upper tracing, the left ventricular pressure curve is recorded simultaneously with the brachial arterial curve, using matched strain gauges in a case of aortic stenosis. In *A*, the paper speed was 25 mm./sec., with time lines every 0.2 sec. At the arrow, the paper speed was increased to 75 mm./sec., and the time lines in *B* were at intervals of 0.04 sec. In *C*, the polyethylene filament was withdrawn from the left ventricle through the mitral valve (*arrow*) into the left atrium. Note the absence of significant gradient between the left atrium and the left ventricular diastolic pressure. The brachial arterial curve is recorded on a different sensitivity in order to facilitate timing of the atrial events.

On three occasions, patients experienced discomfort as the needle pierced the septum. In two patients the discomfort was sharp and localized to the substernal area. In each instance it was of momentary duration and did not recur.

No arrhythmia was noted during the transseptal puncture except for an occasional atrial premature beat. A short episode of ventricular beats usually heralded the entry of the polyethylene catheter into the left ventricle. The procedure has never had to be terminated because of arrhythmia or pain.

The quality of the left atrial pressure tracings was satisfactory (Figs. 3 and 4). The quality of the pressure curves recorded through the small polyethylene catheter was similar to that of those which were recorded percutaneously from the posterior thorax when the latter technique was employed in our laboratory.

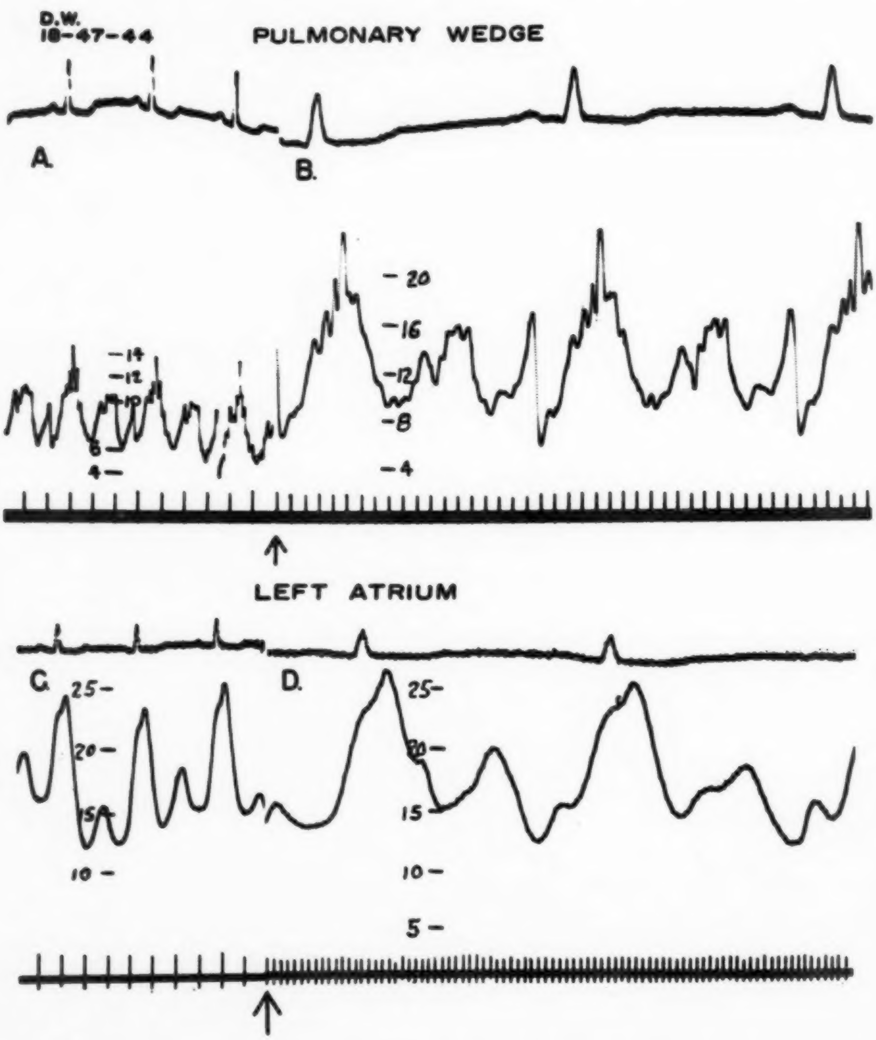

Fig. 3.—The wedge pressure recording in *A* and *B* are compared with the left atrial pressure curve in *C* and *D* obtained during a combined right heart and transseptal cardiac catheterization. Note the similarity of the wave forms. In *A* and *C*, the paper speed was 25 mm./sec. The arrows indicate the change to 75 mm./sec. paper speed in *B* and *D*. In *B*, the time lines were every 0.04 sec., whereas in *D* they were every 0.02 sec. This patient had minimal mitral stenosis, which was confirmed at operation.

Indicator substances can be readily introduced into the left atrium through the transseptal needle.

There have been no serious complications as a result of this procedure. On two occasions, autopsy specimens were examined in patients who succumbed to subsequent complications of their disease. In each instance the interatrial septum was intact, without evidence of defect. Two pin-point areas of hemorrhage on one septum suggested the site of puncture. No areas of hemorrhage were noted in the other septum.

In one patient the puncture inadvertently occurred high in the right atrium, and the needle entered the aorta. There were no subjective symptoms, and the needle was withdrawn without complication or sequelae.

At the time of operation in two patients who were undergoing mitral valvulotomy, blood-stained pericardial fluid was found. It is assumed that the free wall of the left atrium was punctured at some time during the transseptal procedure.

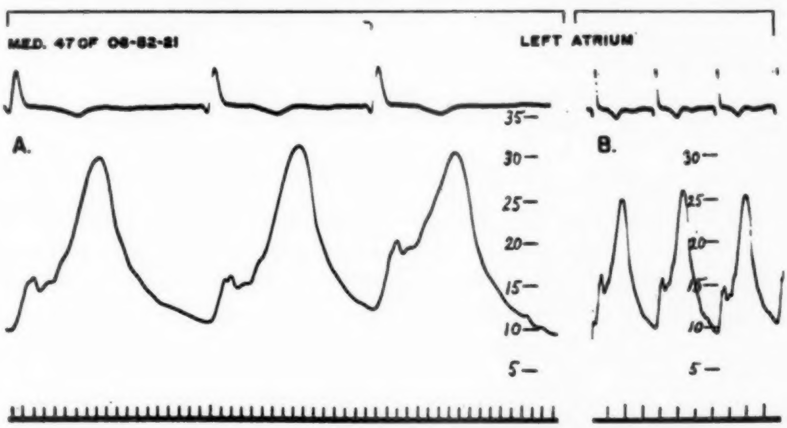

Fig. 4.—A left atrial pressure curve recorded during transseptal catheterization in a patient with predominant mitral insufficiency. In *A*, the paper speed was 75 mm./sec., and in *B* the speed was 25 mm./sec.

DISCUSSION

In our experience, the transseptal technique has proved to be the most convenient and least traumatic method of approach to the left heart. The patient rests comfortably in the supine position and remains basal throughout the procedure. However, certain problems have been encountered. Infrequently, in our early experience, there was difficulty in manipulating the large catheter over the brim of the lesser pelvis. Rotating the body trunk, increasing the intra-abdominal pressure for a period of time and then suddenly releasing it, raising the leg, and placing the patient upright have all been used with variable success. Two attempts failed because of inability to pass this obstruction. After the catheter has been advanced into the right atrium, no difficulty has been experienced in puncturing the atrial wall. Rotation of the hub through approximately 90° facilitates the introduction of the filament catheter through the mitral valve. Since the needle is 4 cm. longer than the catheter, it can be advanced so as to change the location of the needle orifice when difficulty is experienced in passing

the mitral valve. If the left ventricle cannot be entered from the left atrium, it may be punctured from the anterior thorax directly, without changing the patient's position. This procedure was necessary in five cases.

The length, internal diameter, and composition of the plastic catheter are all critical factors for accurate recording of pressure. Although the polyethylene filament catheter is more compliant than the polyvinyl, we found the ease of manipulation and the passage of the polyethylene type to be superior.

Certain advantages have been noted when this technique has been compared to other approaches. The comfortable position of the patient allows accuratr basal measurements and also permits the exercise of one leg or both arms foe stress measurements. Left and right heart catheterization can be carried out utilizing the same vein or as a combined procedure. The need for puncturing extracardiac structures has been obviated. Through the transseptal needle, indicator dilution substances or radiopaque materials may be injected for more complete evaluation. Specimens of blood may be withdrawn from the left heart for complete analysis. In a large number of cases a satisfactory left ventricular pressure curve was obtained.

SUMMARY

Transseptal cardiac catheterization has been performed in 56 patients. In each instance, satisfactory pressure tracings were recorded from the left atrium. The left ventricle was entered in 71 per cent of those cases in which entrance was attempted, and satisfactory data were recorded by means of a polyethylene filament catheter inserted through the transseptal needle.

The advantages of this procedure as a means of obtaining left heart data have been discussed.

ADDENDUM

Since this paper was submitted for publication, 18 additional transseptal procedures have been performed in our laboratory. Our previous findings and results are unchanged after these additional experiences. On one occasion, pericardial tamponade which required multiple pericardicentesis occurred after inadvertent puncture of the aorta from the high right atrial wall. This emphasizes the need for observing exact anatomic relationships in the performance of septal puncture.

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Electrocardiographic Diagnosis of Myocardial Infarction in Cases of Complete Left Bundle Branch Block

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The electrocardiographic diagnosis of myocardial infarction in the presence of complete left bundle branch block has always been recognized as difficult.[1,4] Following the experimental work done by Wilson, many authors have suggested criteria for the diagnosis of infarction occurring under these circumstances.[3,9] Despite much work, the exact scope of these differential criteria is still uncertain. Most studies have been conducted on patients with proved infarction; only a few studies analyze these same electrocardiographic findings in patients without this lesion.

The present study reviews the records of a number of patients with complete left bundle block, complicated or not by myocardial infarction, and attempts to evaluate the changes described as suggestive or indicative of myocardial infarction when this disturbance of conduction is present.

MATERIAL AND METHOD

The present study analyzed the clinical records of 127 patients, most of them seen by us in the San Juan de Dios Hospital since the middle of 1954.

The clinical diagnosis was reasonably certain in all cases, and in 26 it was verified at necropsy. The patients were studied electrocardiographically, by recording the standard leads, the unipolar limb leads, and at least six precordial leads. All the tracings fulfilled the diagnostic criteria established by the American Heart Association for complete left bundle branch block.[10]

Table I shows the age and sex distribution of our patients. The small predominance of females can be explained by the slightly greater number of female patients who consult our outpatient department. Table II lists the frequency of the various etiologies involved in our patients.

We divided the 127 patients into three groups (Table III). *Proved infarction:* Of the 13 cases in this group, 6 were verified at autopsy, 3 on the basis of typical electrocardiographic records without bundle branch block, and the other 4 on the basis of a clinical picture characteristic of myocardial infarction and progressive electrocardiographic changes. *Angina pectoris:* This group included a number of patients with a typical angina syndrome. Some of them had also a history suggestive of previous infarction. *Controls:* None of the patients in this group (87 patients) had signs or symptoms suggestive of angina pectoris or myocardial infarction; 20 of them were autopsied and shown to be free of coronary occlusion or ischemic myocardial lesion.

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RESULTS

For simplification, we have separated the changes observed in QRS from those observed in the S-T segment and in the T wave.

1. *Changes in QRS.*—

Electrical axis: Table IV shows the distribution of the cases in regard to the deviation of the electrical axis of QRS. The axis was determined by measuring the area of QRS in the standard leads.

Right axis deviation, shown by a S_1,R_2,R_3* pattern, was infrequent, but present occasionally both in the records of patients with proved myocardial infarctions and in those of the controls.

A marked left deviation (more than $-30°$), with complexes of the R_1, S_2, S_3* pattern, was seen more frequently in patients with a myocardial infarction but was not exceptional in those without it. In only 2 of the 13 patients with infarction was the R wave in Lead I lower than the S wave in Leads II and III. Since this sign was found to be present in 14 of the 87 controls, it is not, apparently, significant.

TABLE I. AGE AND SEX DISTRIBUTION

AGE (YR.)	MALES	FEMALES	TOTAL
11–20	1	—	1
21–30	3	2	5
31–40	3	5	8
41–50	12	13	25
51–60	12	26	38
61–70	13	24	37
71–80	10	3	13
Total	54 (42.6%)	73 (57.4%)	127 (100%)
Mean age	55.6 ± 2.3	55.3 ± 1.3	55.4 ± 1.2

Cases without axis deviations (R_1,R_2,R_3 pattern*) or with deviation of minor degree ($+30°$ to $-30°$) were the most common, and no difference could be found between the patients with coronary heart diseases and the controls.

Q wave: Small Q waves of short duration were seldom observed in records from patients with left bundle branch block, even in leads obtained from the left side of the precordium. Table IV shows them to be fairly frequent in one or more leads in the patients with myocardial infarction (63 per cent), whereas they were less common in the controls (27.6 per cent). However, further analysis, based on the absolute figures, revealed a greater frequency of the Q wave in one or more leads in patients with bundle branch block without infarction. Of a total of 40 patients with a Q wave, only 8 had infarction (20 per cent), whereas in 24 (60 per cent) this condition could be excluded. It appears significant that 2 of our patients without infarction happened to show a Q wave in Leads aV_F and

*The letters indicate the deflection that corresponds to the largest area; thus, S indicates a predominantly negative, and R a predominantly positive, area.

III in complexes of left epicardial pattern that were predominantly positive. One of these patients showed no evidence of myocardial lesion at autopsy. When Lead I is considered specifically, the appearance of Q might prove to be more important, inasmuch as 5 of 15 patients had suffered a myocardial infarction.

The occurrence of a Q wave in Leads V_5 and V_6 is a very interesting point. We found it present in only 6 of our 127 patients. Of these, one had obvious infarction, a second had doubtful infarction, and in the other 4 this condition could be excluded (3 with autopsy). In 3 of this last group there was a high R wave in Lead V_6 with a single peak and an intrinsicoid deflection at 0.07 and 0.08 second; the Q wave measured 8 mm. and lasted 0.03 second in one case, 0.6 mm. and 0.02 second in another, and 1.2 mm. and 0.02 second in the third. In two of them, left ventricular hypertrophy was discovered at autopsy, and the third also had clinical signs of left ventricular hypertrophy. A fourth patient had Q waves in Leads II, III, aV_F, V_5, and V_6. The Q wave in Lead V_6 measured 0.7 mm., lasted 0.03 second, and was followed by a R wave of low voltage, and the intrinsicoid deflection was at 0.09 second. This latter patient was shown (anatomically) to be free of myocardial disease and significant left ventricular hypertrophy.

TABLE II

ETIOLOGY*	MALES	FEMALES	TOTAL
Arteriosclerosis	38	39	77 (61.5%)
Arterial hypertension	10	38	48 (36.9%)
Rheumatism	9	4	13 (10.7%)
Syphilis	8	1	9 (7.4%)
Primary myocardial diseases	1†	4†	5† (3.3%)
Diphtheritic myocarditis	1†	—	1† (0.8%)
Cor pulmonale (chronic?)	—	1	1 (0.8%)
Unknown	3	3	6 (4.1%)

*In 27 cases, more than one etiology was involved.
†Evidence by necropsy.

Complexes of the *rsR′ or rsR′s′ pattern* in leads that register potentials over the left precordium (or other leads recording similar potentials) have essentially the same values as Q waves, and were present in 4 patients with infarction, but also in 12 others without this lesion. For discrimination this pattern acquired considerable significance in Lead I, for 3 patients of the 8 in whom it was present had myocardial infarction. As already mentioned, complexes of the rsR′ or rsR′s′ pattern and Q waves may be considered clinically to be equivalent and can be examined together. They were present in 8 of the 13 patients with infarction and in only 15 of the 110 patients in whom infarction was uncertain (Figs. 1 and 2).

Polyphasic QRS complexes in Lead III and/or aV_F: Polyphasic complexes (QRS complexes with more than three deflections) were present in 2 of our 13 patients with infarction, but also in 9 of the 87 controls with no evidence of coronary disease (Fig. 2). Three of them were autopsied and found to be free of myocardial infarction.

Aspect of the R wave over the right precordium: Table V illustrates the scant significance that can be attributed to the following changes of this particular wave: the decrease in its voltage or its disappearance in Leads V_1 to V_4, and complexes of the QS or qrS pattern, with a low r wave, as they were encountered in some records of patients without evidence of coronary disease. Nevertheless, it is evident that these changes are relatively more frequent in patients with infarction (58 per cent).

Aspect of the R wave over the left precordium: The following changes in R have been described by some authors as being suggestive of an infarction in the presence of complete left bundle branch block: a second peak of lower voltage in

TABLE III

CLINICAL FINDINGS	NUMBER OF CASES
Myocardial infarction:	
certain	13*
probable	6
possible	3
Angina pectoris:	
typical	12
probable	5
doubtful	7
Without angina pectoris	87 (68.5%)
With cardiac insufficiency	96 (75.6%)

***Six cases proved by autopsy; 3 with a typical electrocardiogram of myocardial infarction in one record, without intraventricular bundle branch block; 4 with typical clinical syndrome of infarction and progressive electrocardiographic changes.**

Autopsy was performed in 26 cases (20.5 per cent).

TABLE IV. CHANGES IN THE QRS COMPLEX

	MYOCARDIAL INFARCTION	ANGINA PECTORIS	OTHERS
Electrical axis of QRS			
+150° to +90°	1	—	2
+89° to +30°	3	4	14 (4)*
+29° to −30°	1	8	33 (7)
−31° to −89°	8	15	38 (9)
$R_1 < S_2 < S_3$	2	—	14 (3)
Q wave present in			
I	5	1	9 (3)
aV_L	7	7	22 (5)
aV_F	1	1	2 (1)
V_4	1	—	1
V_5 and/or V_6	1	1	4 (3)
Total number of cases	8 (63%)	8 (29.6%)	24 (27.6%)

***The number of patients without myocardial infarction at autopsy is given in parentheses.**

Lead V_6 or a slow downward slope of the top. We found them in 16 of the 87 controls and in none of the 13 patients with myocardial infarctions.

RS complex with a broad R and S wave over the left precordium: This change is of significance only when present in more than one precordial lead; otherwise it may be due to the transitional zone and thus be of little value. Although we have found this change in only 3 of our 13 patients with infarction, we are inclined to consider it to be highly significant because it was absent in the records of the controls (Fig. 3).

TABLE V. ALTERATION OF THE QRS COMPLEX

TYPE OF CHANGE	INFARCTION	ANGINA	OTHERS
rsR′ or rsR′s′ pattern			
D_1	3*	–	5 (4)†
aV_L	1	1	6
V_5 and/or V_6	3	–	1 (1)
Total number of cases	4 (31.5%)	1 (3.7%)	12 (13.8%)
Polyphasic complexes in III and/or aV_F	2	3	9 (3)
aV_F predominantly positive	4	1	9 (1)
Precordial leads			
Decreasing voltage of R from V_1 to V_4	7 (58%)	5 (18.5%)	24 (27.6) (5)
Disappearance of R from V_1 to V_4	1	2	3 (1)
qrS or QS with embryonic R wave over the right precordium	2	2	5 (2)
S predominant in V_5	5	6	21 (7)
S predominant in V_5 and V_6	5	1	6 (2)
Notch in S or QS (0.05 sec.)	3	3	10 (1)
RS wave in V_6 with broad R	3	–	–

*One patient showed a complex of qR or QR pattern and disappearance of the first R every time the cardiac frequency increased.

†The number of cases without evidence of myocardial infarction at autopsy is given in parentheses.

Aspect of the S wave in the left precordial leads: A prominent S wave in Lead V_5 can be found with some frequency in each of the three groups, although more often in the group of patients with infarction. (It is certainly more frequent in patients with congestive heart failure.) According to Wilson,[11] this finding indicates only a displacement of the transitional zone.

A prominent S wave in Leads V_5 and V_6 was present in 5 patients with infarction, and in only 7 of the 87 controls.

Changes in the S wave in Leads V_3 and V_4: The sign described by Cabrera and Friedland,[8] i.e., a notch which has a duration of 0.05 second or more at the end of a complex of the rS or QS pattern was found in 10 patients without angina or infarction and in 3 with proved infarction (Fig. 1).

2. *Alterations in the S-T Segment.*—The S-T segment was found to be elevated and convex in the standard and unipolar limb leads in agreement with the major area of QRS in only 2 patients, both of whom had myocardial infarction (Fig. 1).

Elevation of the S-T segment in Leads V_1 and V_2 of more than 0.8 mv. (8 mm.) or more than half the amplitude of T in the same lead (Fig. 2) was registered in 26 patients (Table VI). With the exception of the patients who were receiving digitalis, these changes were seen only in the presence of myocardial infarction.

3. *Changes in the T Wave.*—An inverted symmetrical T wave is relatively rare in patients without clinical evidence of angina or infarction, and, on the other hand, quite frequent in patients with infarction (Table VII). However, this sign does not establish the diagnosis of infarction. Only 4 of the 11 patients who showed this sign has suffered an infarction.

Special attention was paid to the direction of the T wave and its relationship to the major area of QRS. The T wave in cases of left bundle branch block is usually opposite to the major area of QRS. This did not happen in 51 of the 127 patients (40 per cent), but was slightly more frequent in patients with myocardial lesion (58 per cent). However, one must distinguish the cases in which T is opposed to the major area of the ventricular complex with a prominent R wave (R, qR, or Rs pattern) typical of the left ventricular epicardium, from those in which S is prominent over the right precordium. Whereas in the first instance the change in the T wave is unimportant, in the second we found it only in the presence of infarction. Unfortunately, this sign is rare and we have seen it in only 2 patients.

TABLE VI. S-T SEGMENT

	INFARCTION	ANGINA	OTHERS
Deviation of S-T segment in standard and unipolar limb leads, opposing the major area of QRS			
Elevated in Lead I	1	–	–
Elevated in Leads III and aV_F	1	–	–
Total	2	–	–
Elevation of the S-T segment of more than 0.8 mv. (8 mm.) and/or more than half of the height of the corresponding T wave in the precordial leads V_1-V_2			
More than 8 mm.	–	–	3†
More than half the value of T	9*	2†	9†
More than 8 mm. and T/2	–	–	3†
Total	9*	2†	15†

*Four patients under the influence of digitalis.
†All on digitalis therapy.

TABLE VII. T WAVE

	INFARCTION	ANGINA	OTHERS
Perfectly symmetrical (not in transitional zone)	4	1	6 (2)*
Not opposite to the major area of QRS			
I	3	2	12 (2)
II	–	–	1
III	–	1	2
aV_R	2	7	17 (5)
aV_L	–	–	4 (1)
aV_F	–	1	3
V_1 and/or V_2	2	–	—
V_4	–	–	1
V_5 and/or V_6	2	5	17 (1)

*The number of cases without evidence of myocardial infarction at autopsy is given in parentheses.

DISCUSSION

Wilson and his associates,[3,11] on the basis of their experimental work, concluded that in the presence of complete left bundle branch block the electrocardiogram rarely shows any sign definitely suggestive of myocardial infarction. They thought that the left ventricular cavity with this disturbance of conduction is initially electropositive, and, therefore, no Q or QS waves could be registered over the ischemic left ventricle. Since they found the RS pattern normally in the transitional zone in patients without myocardial infarction, they did not attribute much importance to it. Wilson's school showed that an infarction of the ventricular septum caused an initial negativity of the left ventricular cavity, determined by the negativity of the right ventricular cavity during the activation of its free wall. Therefore, in cases of a simultaneous infarction of the interventricular septum and the left ventricular wall, deep Q or QS waves could be recorded over these zones. This theory received clinical-pathologic confirmation by Sodeman and his associates,[12] who observed Q waves in Lead I in 8 patients with left bundle branch block, 6 of whom presented a myocardial infarction, and in 5 of these patients this infarction extended to the interventricular septum.

The school of Sodi-Pallares holds the same opinion.[13] On the basis of their recent research work and clinical-pathologic observations, they consider this disturbance in conduction to be of value in the diagnosis of septal infarction. They even establish correlations between the magnitude and duration of Q and the extension of the septal lesions. On the other hand, Chapman and Pearce[9] are less inclined to accept this sign, since they found it to be present in its typical form in only 3 of 20 patients with an anatomically proved septal infarction.

Our results induce us to question the specificity of the Q wave because we have quite frequently found it in records from patients without clinical or pathologic evidence of myocardial disease. We cannot offer any electrophysiologic explanation for this observation. In some of our patients a Q wave was present in records in which prominent R waves with one peak, a late intrinsicoid deflection, and a broad QRS complex fulfilled all the requisites of complete left bundle branch block; but these records could also be adjusted to the pattern of an intraventricular block due to the left ventricular hypertrophy with a diffuse slowing of conduction in the wall of the left ventricle, and normal activation of the septum.[14] However, one of our patients whose electrocardiogram over the left precordium showed a low, broad, and flat-topped R behind the Q wave, typical of complete left bundle branch block, demonstrated at necropsy a slight left ventricular hypertrophy and no myocardial infarction.

A Q wave in Lead aV_L is relatively frequent and has been observed in our material in 22 of the 87 controls; 10.3 per cent of the controls also showed Q waves in Lead I, so that the appearance of this wave in any electrocardiogram can only be called suggestive of, but does not establish, the diagnosis of myocardial infarction. The same is true for a Q wave in Leads aV_F and III.

Complexes of the rsR′ or rsR′s′ pattern have fundamentally the same significance as a Q wave. We have found them in Leads I, V_5, and V_6 in patients with myocardial infarction, but also in some without it. It could be argued that some controls have had a diffuse septal or mural fibrosis that would electrophysiolog-

ically be equivalent to myocardial infarction, but it must be emphasized that such fibrosis was not found at autopsy. Some authors have stated that a polyphasic QRS in Lead III and/or Lead aV_F could indicate a lesion of the posterior wall in the presence of a complete left bundle branch block. We have come to the same conclusion in regard to this alteration as we did with respect to the Q wave. This QRS configuration, however, was rare in the controls (10.3 per cent).

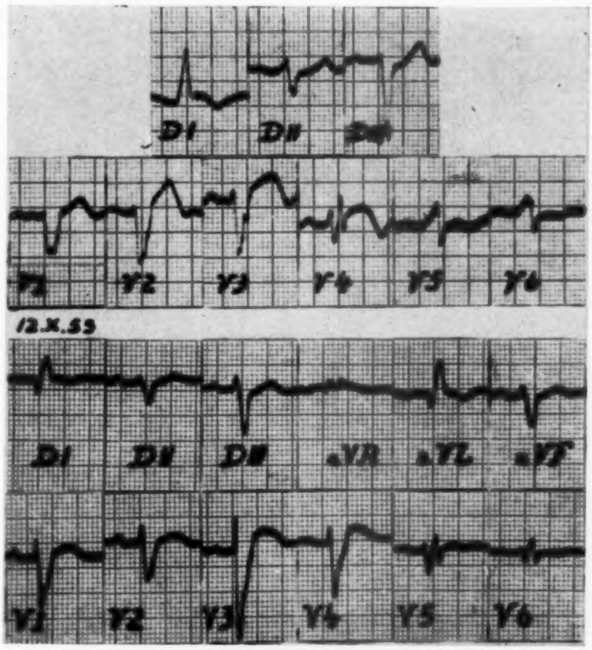

Fig. 1.—Seventy-year-old patient who, on July 24, 1954 (date of the upper tracing), developed a typical episode of myocardial infarction. The diagnosis of complete left bundle branch block was based on the width of the QRS interval (0.15 sec.) and the presence of a normal intrinsicoid deflection in Leads V_1 and V_2, and delayed deflection in Leads V_5 and V_6. The S-T elevation in Lead I and its depression in Leads II and III were signs of acute myocardial infarction, an appreciation further supported by the contour of S-T and T in Lead V_4. The lower record was registered 15 months later and still showed the left bundle branch block. There is a broad and deep Q wave in Leads I and aV_L, and a QRS complex of a rSr's' type in Leads V_5 and V_6, sequelae of an old infarction.

As mentioned before when we reported our findings, the direction of the electrical axis is not suggestive of infarction; neither is a predominantly positive rapid ventricular complex in Lead aV_R. The latter only indicates a marked deviation to the left of the electrical axis of QRS, which is the expression of a ventricular dilatation in most cases. The same applies to an R wave that is lower in Lead I than is the S wave in Leads II and III.

The configuration of R in the right precordial leads, i.e., complexes with prominent S, has no diagnostic importance. The disappearance or lowering of R toward the left, when present in Lead V_1, has been observed in both groups alike and, therefore, lacks diagnostic importance. A prominent S in Lead V_5 only signifies an exaggeration of the frequent shift to the left of the transitional zone in complete left bundle branch block and may arise from cardiac dilatation, since

it appeared more frequently in the presence of cardiac failure. A prominent S wave in all precordial leads could be explained in some way, but is much more frequent in the presence of myocardial infarction (in 5 of 13 patients). But since it occurred in 6 patients of the control group, its diagnostic value becomes questionable.

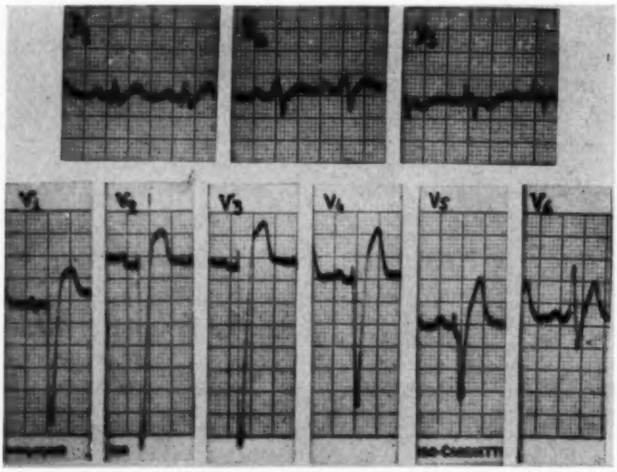

Fig. 2.—Record of a 58-year-old patient in whom necropsy revealed a recent infarction of the apical-anterior region of the left ventricle. There was also left ventricular hypertrophy (580 grams). The tracing was recorded 24 hours before death and 48 hours after the onset of symptoms. The diagnosis of complete left bundle branch block was based on the width of the QRS interval (0.14 sec.), on the shape of the ventricular complex in the precordial leads from Lead V_1 to Lead V_4, and on the delayed intrinsicoid deflection (0.07 sec.) in Lead V_6. Probably other leads such as V_7, V_8, or aV_L would have revealed more clearly the intraventricular conduction disturbance. The aspect of QRS in Lead I (rsR's' type) suggests cardiac infarction, and this was supported by the elevation of the S-T segment in Leads V_1 and V_2 which exceeded the half height of the T wave in the same leads (in absence of digitalis medication).

The configuration of the R wave over the left precordium lacks diagnostic value and will not be discussed here. The appearance of a broad R followed by a broad S in two or more leads over the left precordium or the transitional zone, as it could be described, seems to be useful. We found it in 3 of the patients with infarction and in none of the controls (Fig. 3). Recently, we observed a patient with hyperpotassemia whose electrocardiogram showed a similar configuration over the precordium in so far as QRS was concerned; in the other leads there was no evidence of left bundle branch block, but only changes of the T wave which are typical for this electrolyte disturbance.

Attention has been focused on the S-T segment in the absence of other clues for the diagnosis of a myocardial infarction when complete left bundle branch block is present. Wilson has emphasized that the changes of S-T and T were overshadowed by the alterations due to the disturbance in conduction. Moia and associates[5] were the first to stress the value of the alterations in S-T in cases of recent myocardial infarction. The deviation of the S-T segment opposite to the direction of T, and the inversion of the normal convexity of S-T maintain their diagnostic value in spite of the short duration of these particular alterations.

Dressler and associates[6] in their study confirm the value of the changes of S-T and T and specify their configuration. On the basis of our observations, the deviation of the S-T segment is of significance. In the standard and unipolar limb leads the displacement of the S-T segments toward the major area of QRS could be found only in electrocardiograms of patients with infarction (Fig. 1).

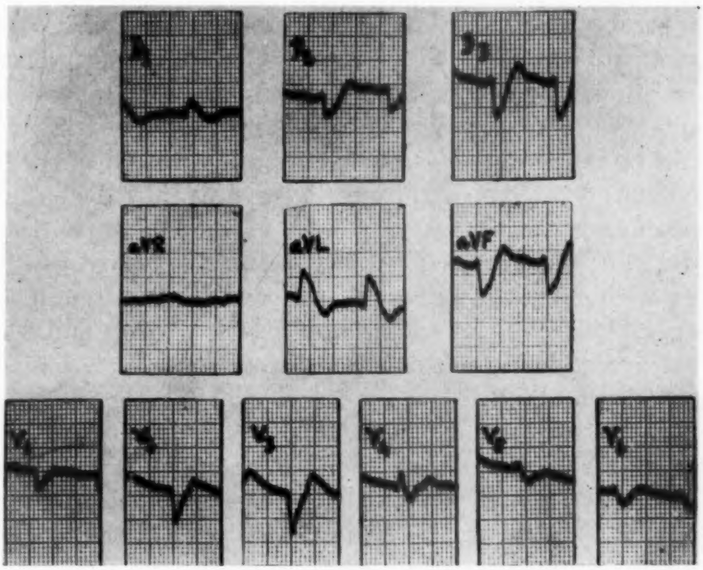

Fig. 3.—Fifty-six-year-old woman in whom necropsy revealed a syphilitic aortitis, stenosis of the coronary ostia, and a recent anteroseptal infarction. The duration of QRS (0.16 sec.) and the aspect of the ventricular complex in Leads I and aV_L gave the diagnosis of complete left bundle branch block. The countour of the QRS waves from Lead V_4 to Lead V_6, with broad R and S waves, were positive signs of myocardial infarction.

Elevation of S-T of more than 0.8 mv. (8 mm.) and/or of more than half the height of the T wave in the same lead in Leads V_1 and V_2 has been observed only in patients with infarction or in those on digitalis therapy (Fig. 2). When these latter patients are discarded, this sign acquires fundamental importance in the diagnosis of myocardial infarction in the presence of complete left bundle branch block. It was found in 15 of the controls, but all of them had received digitalis, whereas 4 of the 9 patients with positive infarction had not received digitalis.

In regard to the evolution of the alteration in the S-T segment, our experience coincides with that of other authors to be indicative of a recent myocardial infarction unless the patient has received digitalis.

Alterations in the T wave arise more often in cases of myocardial infarction with left bundle branch block. This wave assumes a completely symmetrical configuration and fails to be directed opposite to the major area of QRS. Because the same changes can often be found in the electrocardiograms of patients without infarction, such changes lack significance in the opinion of most observers. Nevertheless, we did not find a negative T over the right precordium in the control group, and it was present in 2 of the patients with myocardial infarction.

Thus, a negative T wave over the right precordium is a helpful datum in the diagnosis of this condition.

CONCLUSIONS

In regard to the signs described as indicative or suggestive of myocardial infarction occurring in the presence of complete left bundle branch block, we recognize that most of them often occur in patients with infarction, but may also be seen in the control patients. The frequency with which they appear in patients with infarction obviously depends on the evolution and the site of infarction.

Our analysis questions the specificity of the different signs described as being indicative or suggestive of a myocardial infarction in the presence of complete left bundle branch block, and finds, in general, that the evidence is insufficient to accept such specificity.

There are some exceptions to this general conclusion. For instance, the following signs are highly suggestive of a myocardial infarction in the presence of left bundle branch block: (1) RS configuration with broad R and S waves in more than two leads over the left precordium; (2) displacement of the S-T segment toward the major area of QRS; (3) elevation of the S-T segment in Leads V_1 and V_2 of more than 0.8 mv. (8 mm.) and/or more than half the height of the T wave (unless digitalis is administered); and (4) negative T waves over the right precordium.

In addition to these signs, the evolutive changes of the S-T segment make the diagnosis of a recent infarction certain so long as digitalis therapy can be excluded.

SUMMARY

The electrocardiograms of 13 patients with myocardial infarction and left bundle branch block are analyzed. The diagnosis of the infarction was based on autopsy (6 cases), on typical electrocardiographic changes in some records without the disturbance in conduction (3 cases), and on the typical clinical syndrome and evolutive changes of the S-T segment and T wave (4 cases).

The electrocardiographic changes were compared to those of 87 patients with complete left bundle branch block in whom there was no reason to suspect a myocardial infarction (autopsy in 20 cases), and also to those of 27 patients who were suffering from typical or probable angina pectoris.

All the signs described in the literature as indicating a myocardial infarction in the presence of a left bundle branch block were considered.

The conclusion is that only some changes in the S-T segment and the T wave (particularly if they are evolutive and not explained by the administration of digitalis) indicated with certainty a myocardial infarction. Most of the other signs described, especially those referring to the QRS complex, were found in the absence of a myocardial infarction and, therefore, were not diagnostic.

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Estimation of Residual and End-Diastolic Volumes of the Right Ventricle of Men Without Heart Disease, Using the Dye-Dilution Method

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The principal difficulties in applying the dye-dilution method for the estimation of ventricular volume have been (1) the mixing of dye in the collecting catheter due to the streaming produced by laminar flow,[1-3] and (2) the failure of complete mixing of the indicator in ventricular blood during the first several beats after injection.[4]

Holt[5] estimated ventricular volume in the dog by means of either the dye method or a conductivity cell with injection of hypertonic saline solution as the indicator. End-diastolic volume was estimated either from the peak concentration or from the relationship

$$EDV = \frac{SV}{1 - \frac{C_m}{C_{m-1}}}$$

where SV represents stroke volume calculated from the saline-dilution curve, and C_{m-1} and C_m represent two successive beat-to-beat concentrations of the indicator. Holt's method has been criticized because of the inability to obtain complete mixing of the indicator within the first few beats after injection.[4] The present report describes the results obtained in man by means of a modification of the above-mentioned method.

METHODS

Since catheterization of the right heart in man is technically simpler than is that of the left, it was decided to develop the method first for determining right ventricular volume. Cardiac catheterization was carried out in fasting subjects sedated with 0.5 Gm. of chloral hydrate orally.

Method of Injection.—Under fluoroscopic control, a size 7F Rodriguez-Alvarez injection catheter, 100 cm. long, was placed in the mid-portion of the right ventricle. This is a closed-end

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catheter with six laterally directed openings located 2 to 8 mm. from the distal tip.* Because of fluctuations in pressure in the ventricle, blood will oscillate back and forth near the tip and mix with the contents of the catheter to a certain extent. Since dye was "preloaded" in the catheter and later flushed in with saline, the possiblity existed that a fraction of the dye might be lost prior to injection. To avoid such mixing, .02 ml. of room air was injected into the catheter before the dye. A similar amount of air was injected after the dye. The usual dose of dye was 3.75 mg. Indocyanine green† in 0.75-ml. volume of distilled water.

The preloaded dye was flushed into the ventricle with 12 ml. of isotonic saline by means of a variable-speed, motor-driven injection syringe‡ at a rate of 10 ml. per 0.5 second. The injection was initiated by depressing a foot switch. The latter also indicated the time of injection on the record.

Method of Sampling.—The collection catheter was a 9F Goodale-Lubin type (open end with two side holes 2 mm. from the tip), 100 cm. in length. By notation of the point at which the ventricular pressure pulse changed to the pulmonary arterial configuration the tip of the catheter was placed in the pulmonary artery approximately 2 cm. beyond the pulmonic valves. The other end of the catheter was connected via a three-way stopcock directly to the cuvette of a recording densitometer.§ The physical characteristics of this cuvette, with sharp right-angled bends at the inlet and spreading of the blood path between closely spaced glass plates, favors the dispersion of laminar flow patterns at the point at which the optical density is detected. In order to diminish resistance to flow, the stopcock was drilled out to a diameter of .098 inches. The outlet of the cuvette was connected to a 500-ml. graduated cylinder with large-bore, vinyl tubing. The mouth of the cylinder was closed with a rubber stopper perforated by three openings: one for the connecting tubing from the cuvette, one for tubing leading to a trap and thence to a water-vacuum pump, and the third for connections to a vacuum gauge. Negative pressures of 400 to 700 mm. Hg were used to facilitate rapid withdrawal of blood through the sampling catheter. Rate of flow was determined by timing the collection of blood in the graduated cylinder by means of a stop watch. Flow was adjusted by moving the tip of the catheter slightly or altering the vacuum pressure in order to provide a withdrawal rate of 2.2 ml. per second or higher through the catheter. The volume of the latter was 1.8 or 1.9 ml.

Methods for Obtaining Beat-to-Beat Concentrations.—The downslope of the ventricular washout curve is a "staircase" function (Fig. 1), each plateau representing the concentration in the root of the pulmonary artery during the diastolic interval between heartbeats. The ratio of the concentrations between successive beats was utilized in estimating percentage residual volume. Therefore, it was essential that the differences in concentration should not be distorted or obliterated by excessive mixing within the catheter due to laminar flow, or by a long time constant in the detecting and recording apparatus.

Previous investigations[1-3] as well as our own (Fig. 2) indicated that, when a "spike wave" of dye is suddenly injected into the current of blood flowing through a collecting catheter, elongation of the bolus of dye occurs because of laminar flow. The extent of this elongation varies directly with the length of the sampling catheter and inversely with the velocity of flow through the sampling system. The method used for the determination of the extent of such distortion in the sampling catheter was as follows: blood was drawn from a reservoir through a short length of tubing connected to a "T" or three-way connection, and thence to the cuvette of the recording densitometer. A tuberculin syringe filled with dye was connected to the side arm of the "T" connector.

Various degrees of vacuum pressure were applied to this system in order to provide the desired rates of flow through the cuvette. By "instantaneously" injecting .02 to .03 ml. of dye through the side arm, a small bolus of Indocyanine green could be introduced at will across the flowing

*U. S. Catheter and Instrument Company, Glen Falls, N. Y.

†Cardiogreen, Hynson, Westcott & Dunning, Inc., Baltimore, Md.

‡Brewer Automatic Pipetting Machine, Model 40, Baltimore Biological Laboratories, Inc., Baltimore, Md.

§Gilford Cuvette Densitometer, Model 103-IR, Gilford Instrument Laboratories, Inc., Oberlin, Ohio.

stream of blood. Rate of flow was monitored as described above. Undistorted "spike waves" could not be recorded, since the washout slope always was prolonged (Fig. 2). However, this did not prevent the assessment of distortion due to the sampling catheter, as described below.

After "spike waves" had been recorded at various rates of flow, the catheter to be tested was interposed between the "T" connector and the cuvette of the densitometer. The bolus of dye now traversed the catheter, mixing with its contained blood before entering the densitometer. Recordings of dye-transit curves were repeated at various rates of flow and compared to the curves obtained at similar rates of flow without the catheter. At any given rate of flow the difference between the 95 per cent disappearance times with, as compared to without, a catheter in the system was taken as the index of distortion produced by laminar flow in the catheter. For example, Fig. 2 shows that at a blood flow of 2.4 ml. per second in the system the delay in 95 per cent disappearance time caused by introducing a catheter which was 100 cm. in length and had an internal volume of 1.9 ml. was 0.7 second. The results indicated that in order to obtain 95 per cent disappearance time in 1.0 second or less, it was necessary to achieve a rate of flow through any given catheter which was greater than 1 times its internal volume per second.

Fig. 2 indicates that the principal distortion produced by laminar flow in the sampling catheter is prolongation of the exponential washout slope. When sampling is done from the pulmonary artery after injection of dye into the ventricle, the exponential tail of dye concentration from one cardiac cycle will mix in the catheter with the advancing front of dyed blood sampled during the succeeding cycle. Such mixing can obliterate the plateaus in the dye-concentration curve if velocity of flow in the sampling catheter is inadequate. By maintenance of a flow of 2.2 ml. per second or higher through a 9F, 100-cm., collecting catheter (internal volume of 1.9 ml.) attached directly to the cuvette by means of a large-bore stopcock, a 95 per cent disappearance rate of 0.8 second or less was achieved in the test system described above. It is apparent that the slower the heart rate, the less distortion will appear.

The 95 per cent response time of the densitometer was decreased to .02 second by reducing in value the capacitors in the two-section, low-pass filter circuit of the densitometer.* This modification resulted in the appearance of 120-cycle interference (Fig. 1). However, the latter did not prevent accurate readings of relative concentrations. Since the shortened time constant resulted in improved delineation of the dye curves, attempts to eliminate the high-frequency interference with external filtering were abandoned.

Method for Estimating Residual and End-Diastolic Volumes.—The studies of Irisawa, Wilson, and Rushmer[4] indicated that in the dog, mixing of indicator was complete by the third cardiac cycle after injection in approximately 80 per cent of the animals with heart rates below 110 beats per minute. Consequently, the ratio between the fourth and third beats was used in the present study, except in those instances in which washout of dye was too rapid to permit accurate measurement of concentrations at this time. In such cases the ratio of concentrations used was the latest cycle-to-cycle concentration that permitted accurate readings.

If mixing is complete and stroke volume is constant, the ratio of concentrations $\left(\frac{C_m}{C_{m-1}}\right)$ is an estimate of the percentage residual volume.[5,10] For example, if the ventricle empties completely, the ratio will be zero; if it empties 50 per cent, the dyed ventricular blood during the succeeding beat will be diluted by half, resulting in a ratio of .50, etc. Similarly, the number of beats required to produce 95 per cent disappearance of peak concentration at an assumed constant stroke and residual volume will depend on the residual volume as a percentage of the end-diastolic volume. Thus, at a constant residual volume of 50 per cent the concentration of dye in the next cardiac cycle past the peak will be 50 per cent of the peak concentration. In succeeding cycles it will be reduced to 25, 12.5, and 6.25 per cent. Thus, 95 per cent washout time will require slightly more than 5 cardiac cycles, including the peak-concentration cycle. This method of estimation provides an approximate check on the percentage residual volume obtained from the ratio of concentrations between the fourth and third cycles, provided that residual volume is reasonably constant.

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*We are indebted to L. A. Marzetta, Electronic Instrumentation Section, National Bureau of Standards, Washington, D. C., for these modifications.

Stroke volume was estimated by dividing the cardiac output per minute by the heart rate. The cardiac output was obtained by sampling from the brachial artery in the conventional manner. With a polyethylene connecting catheter connected from the brachial arterial needle to the side arm of the three-way stopcock at the inlet of the recording cuvette, it was possible to record the cardiac output from the same bolus of dye used for determining right ventricular volume. Inscription of the latter dye curve usually was essentially complete at the end of 5 seconds, thus permitting sufficient time to record both curves in sequence. In order to prevent excessive loss of blood, and also because the high vacuum pressure resulted occasionally in instability of the recordings from the brachial artery, a conventional motor-driven withdrawal syringe was substituted for the vacuum pump. A large-bore, three-way stopcock on the outlet side of the densitometer cuvette was turned at the appropriate time to connect this pump. It should be noted that the determination of cardiac output is not essential to the estimation of percentage residual volume in the present method.

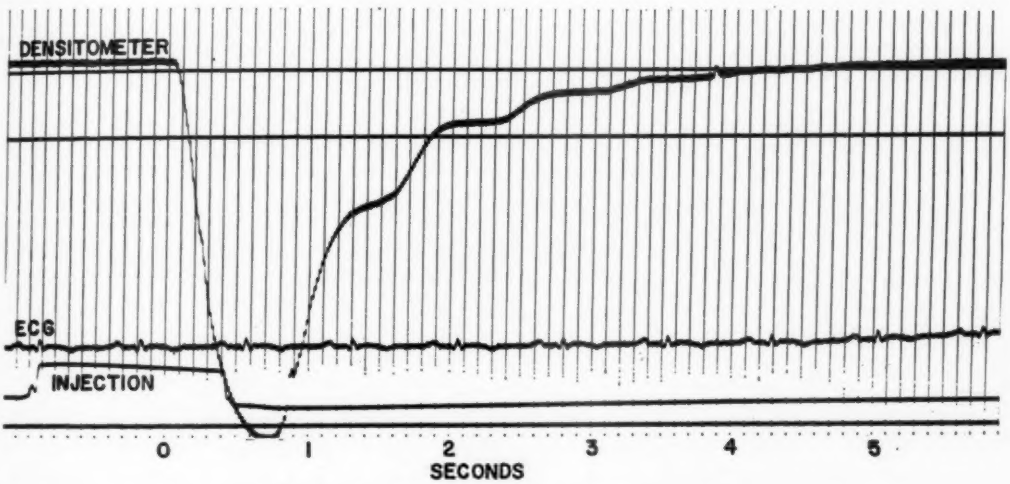

Fig. 1.—Dye-dilution curve in Subject L.O. Injection in right ventricle and sampling from pulmonary artery. Volume of catheter, 1.8 ml. Sampling rate, 2.5 ml. per second.

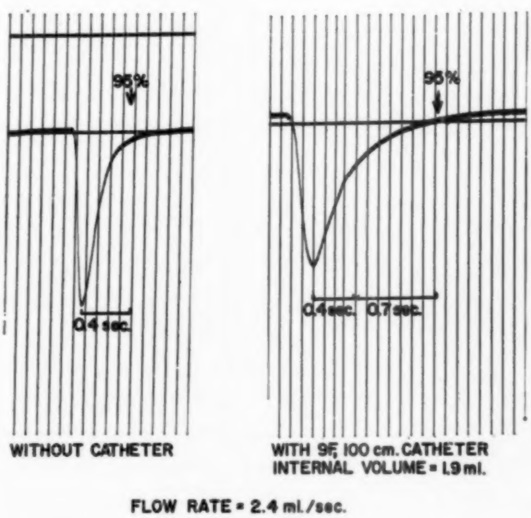

Fig. 2.—Broadening of "spike wave" input of dye by passage through sampling catheter. See text for details.

TABLE I. ESTIMATED RESIDUAL AND END-DIASTOLIC RIGHT VENTRICULAR VOLUMES IN SIX MEN WITH "NORMAL" HEARTS

SUBJECT	DIAGNOSIS	AGE (YR.)	SURFACE AREA	PRESSURES (MM. Hg)		RESIDUAL VOLUME PER CENT		HEART RATE (PER MIN.)	STROKE VOLUME (ML.)	EDV (ML.)	EDV/CM.^{2} OF SURFACE AREA
				R.V.	P.A.	C_{m4}/C_{m3}	95% WASH-OUT TIME				
J. P.	Cirrhosis	44	1.88	26/3	23/6	45 45	42 46	85 82	91 95	166 173	88 92
J. B.	Peptic ulcer	42	2.07	30/4	25/8	41 52	43 52	70 70	72 72	122 150	59 72
G. L.	Compensated emphysema	65	1.74	24/2	22/6	40 43	47 48	100 100	57 64	95 112	55 64
E. S.	Pyelonephritis	44	1.91	32/4	32/12	40 50	48 48	66 63	91 96	152 192	80 100
A. H.	Benign prostatic hypertrophy	75	1.40	28/4	23/10	55	55	100	52	116	83
F. B.	Bronchogenic carcinoma	65	1.75	32/3	32/12	54	55	104	79	172	98
Mean		55	1.79	30/3	26/8	46.5	48.4	84.0	77.9	145.0	79.1
Standard deviation						5.4	4.1	16.1	16.1	32.0	16.2

RESULTS

The percentage residual volume was obtained in 10 adequately high velocity, catheter-flow, determinations on 6 subjects without history of heart disease or cardiac enlargement, as ascertained by roentgenography, and with essentially normal right heart pressures (Table I). As estimated by the ratio C_{m4}/C_{m3}, the residual volume averaged 46.5, S.D. = 5.4, per cent of the end-diastolic volume in the 12 determinations. As estimated by the 95 per cent washout time, the residual volume averaged 48.4, S.D. = 4.1, per cent. If the mean values for each subject were taken, the average residual volume for the 6 subjects was 47.8, S.D. = 5.1, per cent, as calculated by the ratio method, and 49.4, S.D. = 4.2, by the 95 per cent washout time.

The heart rate in the different subjects varied from 63 to 104 (mean 84.0, S.D. = 16.1) beats per minute. The mean stroke volume was 77.9, S.D. = 16.1, ml. per beat. Estimated end-diastolic volume averaged 145.0, S.D. = 32.0, ml. in the 6 subjects, and end-diastolic volume per unit surface area averaged 79.1, S.D. = 16.2 ml. (Table I). If the mean values for each subject were used, the average end-diastolic volume was 147 ml., S.D. = 31.

The effect of breath holding was determined in 2 of these subjects (G. L. and E. S.). In Subject G. L., breath holding at the end of a normal inspiration resulted in a decline of estimated residual volume from 41 to 25 per cent. In the same subject, breath holding at the end of a normal expiration also produced a decrease in residual volume to 25 per cent. In Subject E. S., breath holding after a deep inspiration was measured twice. This maneuver resulted in a fall in estimated residual volume from a mean value of 45 per cent during normal respiration to breath-holding values of 25 and 23 per cent, respectively. Calculation of per cent residual volume from the 95 per cent washout time provided similar values.

DISCUSSION

In the absence of sampling from two separate sites in the ventricle it is impossible to be certain that complete mixing has been achieved in the ventricular cavity. Because of the trabeculated surface of the ventricular wall and the elongated configuration of the ventricular cavity, it is possible that there are portions which do not mix entirely during the diastolic interval. If the end of the injection catheter lies centrally in the ventricular space, it is possible that dye would not be distributed into these dead spaces during the first cardiac cycle. To obviate this possibility, high-pressure injection of dye was employed with 12 ml. of saline wash. Preliminary experiments indicated that high-velocity injection frequently produced ventricular ectopic beats in the dog heart, but in the human heart this event was rarely encountered. If the catheter tip should lie near the ventricular wall, then a portion of the dye could be injected into the pockets of the trabeculated inner lining and mix only after several beats with the ventricular contents.

It seems improbable that ventricular mixing has not occurred after several beats. Irisawa's experience[4] in the dog indicates that, at comparable heart rates, mixing does occur in the majority of instances by the third beat. However, even

if the dye is mixed by the third beat, the incoming undyed blood entering from the atrium cannot be relied upon to enter and mix completely with all of the more stagnant areas in the ventricular cavity. In such an event the ratio of C_{m4}/C_{m3} will be smaller than it would be if the incoming blood were evenly dispersed. Thus, if there is an error in this method, it most likely will be in the direction of underestimating rather than overestimating the residual volume. The good agreement with the estimate obtained from the 95 per cent washout time suggests but does not prove that this error is quite small. The latter method probably is only approximate, since it assumes constant percentage residual and stroke volumes from the peak concentration to 95 per cent disappearance.

The relatively small standard deviation of the estimated percentage residual volume suggests that the normal individual in the resting state has a residual volume between 40 and 55 per cent of the end-diastolic volume, although the series is too small to define normal limits. Using a similar method, Holt found an average residual volume of 55 per cent in the left ventricle,[5] and 57 per cent in the right ventricle,[6] of the dog. Other methods of determining the percentage residual volume from the correlation of roentgenograms with the volume of cardiac tissue at postmortem examination[7-9] or by the slope of the dye-disappearance curve obtained with slow withdrawal of dyed blood through long catheters[10] contain too many unknown variables to be regarded as more than crude approximations.

Despite the approximate nature of the x-ray method, Nylin[7] carried out many valuable studies, which included the observation that the Valsalva maneuver considerably reduced the residual volume of the heart. In addition, Rushmer[11] showed that breath holding either in inspiration or expiration was a sufficient Valsalva maneuver to significantly decrease the size of the heart, as determined by roentgenography. Rushmer found that the decline in heart volume resulted from compression of the large veins in the chest, thereby blocking venous inflow. Using biplane angiocardiography in 2 human subjects in the sitting position, Bruce and Chapman[12] reported left ventricular residual volumes of approximately 24 per cent of the end-diastolic volume. These values agree with the percentage right ventricular residual volumes observed in the 2 subjects of the present series during breath holding. If breath holding was employed during angiocardiography, it is possible that the low residual volume estimated by their method may have been due to this factor. It also could have been due to body position, since Nylin's studies indicate that the change from the supine to the erect position decreases the end-diastolic volume of the heart.[7]

The somewhat greater variability of the estimated end-diastolic volume as compared to the percentage residual volume was a consequence of the variation in stroke volume, which, in turn, was dependent upon considerable differences in heart rate and cardiac index among the different subjects. Estimated end-diastolic volume varied between approximately 100 and 200 ml. in the 6 subjects. On the basis of correlation between roentgenographic studies during life and the postmortem measurement of the volume of cardiac tissue, Nylin estimated the end-diastolic blood volume of the normal heart to average approximately 540 ml.

Assuming that the four chambers have approximately equal volumes, this would indicate an end-diastolic volume of the right ventricle of approximately 135 ml., a value not far removed from the present estimate of 147 ± 31 ml.

A method for estimating percentage residual volume which does not depend upon sampling through a long catheter would be highly desirable. Substitution of a conductivity cell near the end of the catheter as the sensing element and injection of hypertonic saline as the indicator has been used to measure ventricular volume in animals[4,5] and should be applicable to man. The attainment of high-velocity flows of blood through the collecting catheter which is essential to the present method is technically difficult. Furthermore, some smearing of the dye curve is unavoidable with long sampling catheters, even under ideal circumstances. An additional improvement in the method would be the substitution of one double-lumen catheter for the two separate injection and collection catheters used at present. The double-lumen catheter should be designed so as to permit injection of the tracer substance through multiple ports facing in different directions, in order to provide rapid mixing with the ventricular blood volume. Various approaches to these problems are under study in this laboratory.

SUMMARY

Right heart residual and end-diastolic volumes have been estimated by the dye-dilution method. Various modifications have been introduced in order to obtain reasonable approximations. These include attainment of high-velocity flows through the sampling catheter, shortening of the time constant of the recording densitometer, measures to insure optimal mixing of the injected dye in the ventricular cavity, and estimation of the percentage residual volume both from the ratios of beat-to-beat concentrations in the later part of the dye-disappearance curve and from the number of cardiac cycles required to obtain 95 per cent washout of dye. Cardiac output was estimated by means of brachial arterial sampling in the conventional manner, and the end-diastolic volume was calculated from the stroke volume so obtained and the percentage residual volume.

In 6 subjects with no history of heart disease, normal right heart pressures, and normal-sized hearts as determined by roentgenography, the end-diastolic volume averaged 147 ± 31 ml. The estimated residual volume averaged 48 ± 5 per cent of the end-diastolic volume. In 2 subjects studied, breath holding reduced this value to 25 per cent.

We wish to thank Miss M. J. Taylor for valuable technical assistance and for useful suggestions toward improving the method.

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Experimental and Laboratory Reports

The Local Effect of Carbon Dioxide on Human Blood Vessels

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Although it is generally assumed that carbon dioxide exerts a local vasodilator action on blood vessels, the direct evidence is scanty. The evidence in animals consists principally in the depressor action of mixtures of carbon dioxide, when used to ventilate the spinal animal.[1,2] In man, the general circulatory disturbances caused by breathing mixtures of carbon dioxide cannot be eliminated, and they overshadow the local effects of carbon dioxide. Local administration must be used. Immersion of the calf of the leg[3] or the hand[4,5] in water saturated with carbon dioxide has been found to increase the flow of blood as measured by venous occlusion plethysmography or calorimetry; the increase ranged from 15 to 150 per cent. It is not known whether, in these experiments, the carbon dioxide exerts its effect by diffusing through the skin and acting on the vessels, or by stimulating sensory nerve endings and exciting an axon or other reflex.

It is clearly desirable to observe the effect of carbon dioxide delivered more directly to the blood vessels. Unfortunately, it is not easy to devise a satisfactory experiment in which carbon dioxide is added to the arterial blood which supplies a limited part of the body. In preliminary experiments in this department with Dr. R. F. Whelan, we found that intrabrachial injection of carbon dioxide dissolved in saline causes an increase in the flow of blood in the forearm, but that this is nearly matched by control injections of saline free of carbon dioxide, and it is difficult to separate the effect of carbon dioxide from the larger effect of the saline itself. The effect of the saline is probably due to the reduced viscosity of the diluted blood. Infusion of gaseous carbon dioxide into the brachial artery[6,7] causes a great increase in the flow of blood in the forearm and the hand, but this is due to the vasodilator action of gas embolism, and is not due to a specific action of carbon dioxide. Oxygen which is injected in the same way is equally effective. In the present investigation, therefore, carbon dioxide was adminis-

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tered by subcutaneous injection. Changes in the circulation were followed by measurements of the temperature of the skin. The results of some of these experiments have already been briefly reported.[8]

METHODS

The subjects sat comfortably with the forearms bare in a room at a constant temperature between 16° C. and 17.5° C. Observations were made of the temperature of the skin at 10 points on the ventral surface of the forearm; the distribution of the points is shown in Fig. 1, and care was taken to place them so that none was over a large vein. In many experiments, observations were also made at two points, corresponding to point numbers 5 and 7, on the ventral surface of the opposite forearm. The site of injection was about midway between the wrist and the crease of the elbow. Before the procedure was started, the skin over the site of injection was sterilized. The circulation was arrested at both wrists for the duration of the experiment by cuffs at 200 mm. Hg, so that the temperature of the skin of the forearm was unaffected by fluctuations in the flow of blood through the hands. Measurements of temperature were then made at each point in rotation; a complete cycle of readings took 2.5 minutes. Readings were continued until three consecutive measurements at each point were in good agreement. Experiments were abandoned in the few cases in which they could not be completed in 40 minutes; this was the maximum time for which it was thought to be advisable to arrest the circulation to the hand.

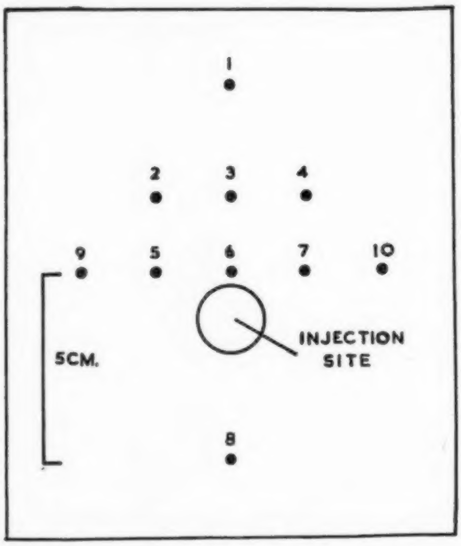

Fig. 1.—Points marked on the ventral surface of the experimental arm. Observations of temperature were made in rotation; a complete cycle took 2.5 minutes.

When conditions were stable, the first of three injections of 10 ml. of gas was made subcutaneously. Care was taken to be sure that the needle was not in a blood vessel. With experience, it was possible to make the injections at a depth in the subcutaneous tissues at which the gas spread widely without causing discomfort. Measurements of temperature were then continued for 3 cycles (15 minutes), and the second injection was given, if possible, through the same site of injection as the first. This was desirable, first, to save discomfort and, secondly, to prevent escape of gas. The measurements of temperature were resumed for 3 more cycles, the third injection was given, and 3 more cycles then completed the observations.

For the injections, "Atlas" all-nylon syringes with a standard rubber piston ring were employed; these are almost free of leakage. Fine hypodermic needles were used, and after the preliminary experiments a new needle was used for each injection.

RESULTS

The pattern of distribution of the injected gas varied between individuals, but was reasonably consistent in any one person. The gas made a local irregular subcutaneous pocket, up to 10 cm. long and 5 cm. wide, and a greater or lesser quantity entered the perivenous connective tissue, tracking beside the veins, sometimes down to the wrist and up to or above the crease of the elbow.

Preliminary experiments showed that whereas carbon dioxide disappeared rapidly, and was largely absorbed in 5 minutes, air was very persistent. Therefore, a gas was sought for control injections which disappeared at a rate which was judged to be similar to that of carbon dioxide. Nitrous oxide was found to answer this purpose. It has a molecular weight, solubility, and diffusibility very similar to those of carbon dioxide.

Main Series of Experiments.—Three subjects were used, and each was, on different occasions, injected with 0, 12.5, 25, 50, and 100 per cent carbon dioxide; the diluting gas was, on every occasion, nitrous oxide. The results of a typical experiment are shown in Fig. 2. A total of 30 ml. of 100 per cent carbon dioxide

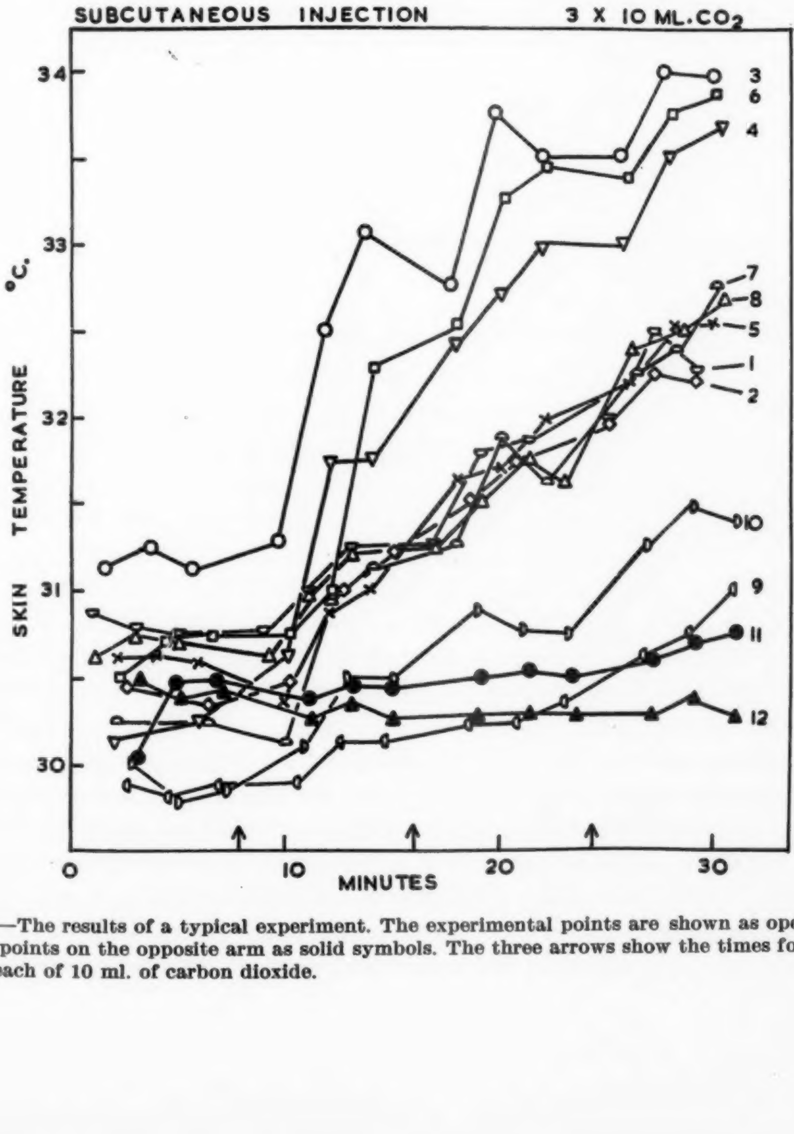

Fig. 2.—The results of a typical experiment. The experimental points are shown as open symbols, the control points on the opposite arm as solid symbols. The three arrows show the times for the three injections, each of 10 ml. of carbon dioxide.

was injected into the subcutaneous tissues. There was a rise in temperature at each of the observation points in this arm. The rise was greatest at points 3, 4, and 6, and least at points 9 and 10. But even at points 9 and 10 the rise was very much larger than at points 11 and 12, the points on the control arm. In fact, at point 12 the temperature was very slowly falling. It is clear that the effect of the injection is to cause a rise in temperature in the adjacent skin.

TABLE I. EFFECT OF SUBCUTANEOUS INJECTION OF 3 × 10 ML. CARBON DIOXIDE

POINT	MEAN RISE IN TEMPERATURE (°C.)
1.	0.87
2.	0.82
3.	2.02
4.	2.22
5.	1.02
6.	1.95
7.	1.35
8.	1.32
9.	0.50
10.	0.97
	Mean 1.30
11.	0.05
12.	−0.22
	Mean −0.09

Mean rise in experimental arm above temperature in the control arm: = 1.30 − (−0.09)
= 1.39°C.

If for each point the mean of all observations of temperature made after the first injection of gas is compared with the base-line observation of temperature before the first injection, we get the results shown in Table I. The mean rise in temperature at all the points in the injected arm is 1.30° C., the mean rise at the points in the control arm is −0.09° C., so that the rise attributable to the injection is 1.39° C.

The results of this and fourteen other experiments of the same type are summarized in Table II, and the rise in temperature attributable to the injections is shown in Fig. 3,*A*. It is clear that the percentage of carbon dioxide in the injected gas has an important effect on the changes which result in the temperature of the skin.

Preliminary Experiments.—A set of fifteen preliminary experiments duplicated the main series of experiments in all respects except two. First, less attention was paid to the needles, and a new needle was not employed for each injection. Secondly, observations were not made at points 11 and 12 on the control arm. At the time these experiments were performed it was proposed to use the outlying points 8, 9, and 10 as reference or control points, because it was thought that the effect of the injection would not spread to these. But as

can be seen from Fig. 2, these outlying points participate in the rise in temperature, and these experiments are, therefore, incomplete in the sense that there are no valid reference points.

The conditions of the experiments were, however, identical to those of the main series, in which no considerable drift was found in the temperature at the reference points (Table II), and it has therefore been thought worth while to show, in Fig. 3,*B*, the mean rise in temperature at the 10 points on the injected arm (corresponding to column 1 in Table II). It can be seen that these results confirm the main features in Fig. 3,*A*.

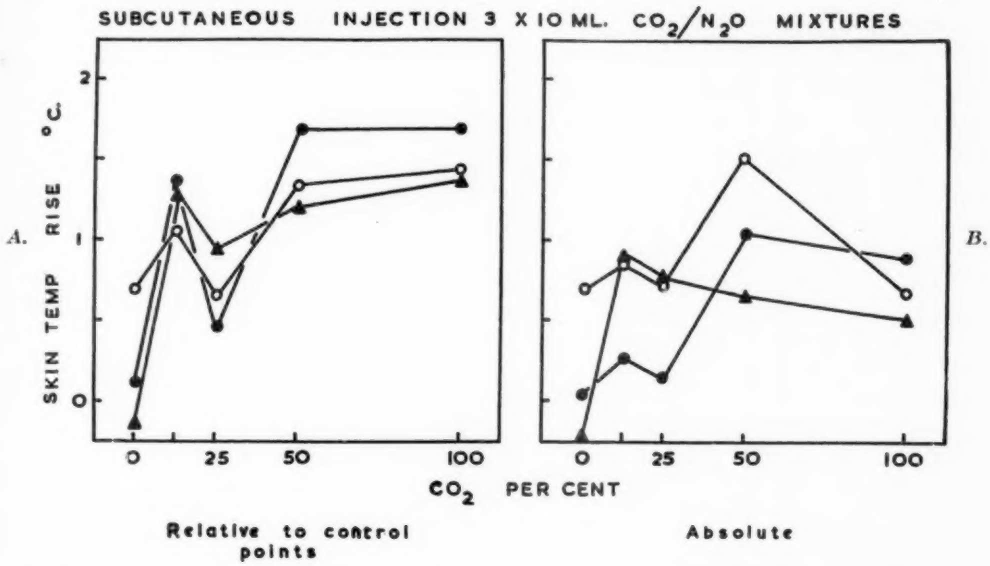

Fig. 3.—*A*, Results of the main series of experiments on three subjects. *B*, Results of the preliminary experiments on three subjects: ○ = S.E.G.A. ▲ = A.D. ● = A.D.M.G.

All these results indicate a difference between the effects of injecting carbon dioxide and the effects of injecting nitrous oxide. Two explanations could be advanced. First, carbon dioxide may be a vasodilator substance and nitrous oxide inert. Secondly, the rise in temperature may be due to the trauma of injection, and nitrous oxide may suppress this vasodilatation, whereas carbon dioxide permits it to occur. It is unlikely that nitrous oxide behaves in this way, but it would be remarkable if the behavior were shared by other gases. Accordingly, it was decided to test the effect of cyclopropane and air. Cyclopropane is a soluble gas that might be expected to disappear at a rate similar to that of carbon dioxide. The results are included in Table II. In two experiments, cyclopropane caused a rise in temperature slightly greater than that caused by nitrous oxide, but very much smaller than that caused by pure carbon dioxide. There is insufficient evidence to judge whether the difference between cyclopropane and nitrous oxide is real or fortuitous, but it appears that the injection of neither gas has an appreciable effect on the blood vessels.

This conclusion is confirmed by the results of three experiments in which air was injected subcutaneously. In none of these was an appreciable rise in

Table II. Changes in Temperature of Skin (°C.) After Subcutaneous Injections of Gas

	SUBJECT									MEAN		
	S.E.G.A.			A.D.			A.D.M.G.					
	1	2	3	1	2	3	1	2	3	1	2	3
CO_2 (100%)	1.10	−0.32	1.43	1.31	−0.09	1.40	1.61	−0.09	1.70	1.34	−0.17	1.51
CO_2 (50%)	1.05	−0.29	1.34	0.94	−0.26	1.20	1.43	−0.26	1.69	1.14	−0.27	1.41
CO_2 (25%)	0.42	−0.22	0.64	0.54	−0.40	0.94	0.21	−0.24	0.45	0.39	−0.29	0.68
CO_2 (12.5%)	0.94	−0.12	1.06	1.19	−0.09	1.28	0.96	−0.40	1.36	1.03	−0.20	1.23
N_2O (100%)	0.56	−0.12	0.68	−0.11	0.05	−0.16	0.01	−0.11	0.12	0.15	−0.06	0.21
Cyclopropane (100%)	—	—	—	0.14	−0.26	0.40	0.00	−0.28	0.28	0.07	−0.27	0.34

Column 1: Experimental.
Column 2: Control.
Column 3: Change attributable to injected gas.

temperature observed. The air was slowly absorbed. The slight uncertainty in interpreting the experiments using injected air was due to the belief that continued distention of the tissues by the persistent presence of the air may have mechanically interfered with a vasodilator response; the air may have compressed the vessels. This possibility was tested by the experiments shown in Fig. 4. The effect of a subcutaneous injection of 10 μg of histamine into a region which 8 minutes previously had received a subcutaneous injection of 10 ml. of air was compared with the effect of an identical injection of histamine into the opposite forearm. The histamine caused a rather larger and more widespread rise in temperature on the side that had received the air. The flare in one experiment was as large on the side into which air had been injected (25 sq. cm.) as on the control side (25 sq. cm.). In a second experiment, after an injection of 20 ml. of air, the flare due to histamine was more extensive on the injected (47 sq. cm.) than on the control (34 sq. cm.) arm. Thus, the injection of air does not suppress the vasodilatation due to histamine. It can be concluded that after the injection of air the persistent presence of the air did not suppress or mask a vasodilator response to the trauma of the injection.

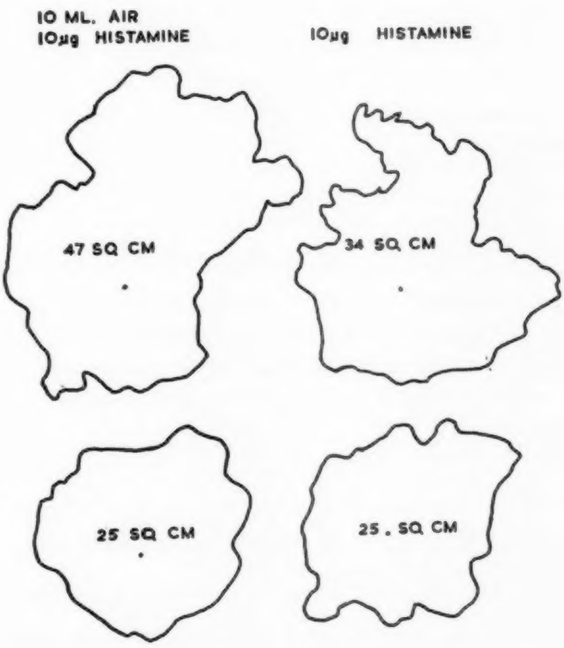

Fig. 4.—The areas of histamine flares obtained in two experiments. On the left are the flares obtained in the experimental forearms, and on the right are those obtained in the control arms.

DISCUSSION

After subcutaneous injection of carbon dioxide, in concentrations from 12.5 to 100 per cent, there is a local rise in the temperature of the skin, which indicates a vasodilatation in the resistance vessels. This vasodilatation is not seen after injections of nitrous oxide, cyclopropane, or air, but the injection of

air does not prevent the dilatation due to histamine. From this it is concluded that nitrous oxide, cyclopropane, and air, three quite different gases, do not suppress a hypothetical vasodilatation in response to the trauma of the injection. Therefore, the dilatation caused by carbon dioxide is considered to be due to the presence of the gas, and not to the trauma of injection.

The results indicate that carbon dioxide has a vasodilator action at all concentrations tested. The method of administration is, unfortunately, an extremely crude one, and there is no indication of the concentration of carbon dioxide at the wall of the blood vessel which may result from diffusion from the various mixtures used. The definite vasodilator action of 12.5 per cent carbon dioxide, however, suggests that carbon dioxide may have a vasodilator effect within the physiologic range of tensions.

A conspicuous difference was noticed between the vasodilator action of carbon dioxide and that of histamine. Carbon dioxide caused a widespread rise in the temperature of the skin, but only a slight general reddening of the skin. A dose of histamine which, when injected subcutaneously, caused a similarly widespread and large rise in the temperature of the skin caused also a very large and conspicuous flare. Even one hundredth of this dose of histamine, which caused a restricted and much smaller rise in the temperature of the skin, caused a conspicuous flare. From this it appears that the action of carbon dioxide is very largely on the resistance vessels which control the flow of blood, and is less pronounced on the vessels responsible for the content of blood in, and the depth of color of, the skin.

SUMMARY

1. Injections of 12.5 to 100 per cent carbon dioxide under the skin of the forearm cause a fairly widespread local vasodilatation.

2. This vasodilatation is due to the vasodilator action of the carbon dioxide, and is not a consequence of the trauma that accompanies the injections.

3. The action of carbon dioxide affects principally the resistance blood vessels.

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The Effect of Norepinephrine on the Digital Veins

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The digital rheoplethysmograph is a sensitive recorder of digital blood flow.[1,2] It has been shown recently that the pre- and postcapillary vessels of the digit have the ability to constrict and dilate independently of one another, much as do the afferent and efferent glomerular arterioles of the kidney.[3] Therefore, it was considered of interest to study rheoplethysmographically the effect of norepinephrine on the digital veins, to learn whether or not the drug constricts the postcapillary as well as the precapillary digital vessels.

MATERIALS AND METHODS

Ten subjects (6 men and 4 women) who ranged in age from 32 to 65 years (mean of 46 years) were studied. Three were white persons and 7 were Negroes. None of the subjects had significant cardiovascular disease. All observations were made in a comfortable air-conditioned room (77° F.; relative humidity, 50 per cent). Rheoplethysmograms (RPG) were obtained by methods previously described.[1,2] The subjects rested in a hospital type of bed, with the right arm passively supported by a special arm rest, and with the digit under study, the right index finger tip (2RF), at heart level.

An infusion bottle which contained 500 c.c. of a sterile 5 per cent solution of glucose in water, and another bottle which contained 4 c.c. of a sterile 0.2 per cent solution of norepinephrine* in 500 c.c. of normal saline were connected by means of a three-way stopcock to an indwelling needle placed in the left antecubital vein. This made it possible to switch the infusions without the subject's awareness of the change. In some of the subjects, arterial pressures or central venous pressures were recorded simultaneously with the RPG. After control recordings had been obtained while the glucose solution was flowing into the vein, norepinephrine was infused at a rate of 30 drops a minute until a desired vascular response was obtained. The RPG was recorded uninterruptedly from the time the infusion of norepinephrine was stopped until recovery was complete.

RESULTS

The results are summarized in Figs. 1 and 2 and Table I. The arterial blood pressure rose in all subjects; the average increase in systolic pressure was 47 mm. Hg, and the average increase in diastolic pressure was 17 mm. Hg. A bradycardia developed in all subjects; the mean length of the pulse cycle increased from 0.80 to 0.95 second.

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*Levophed bitartrate.

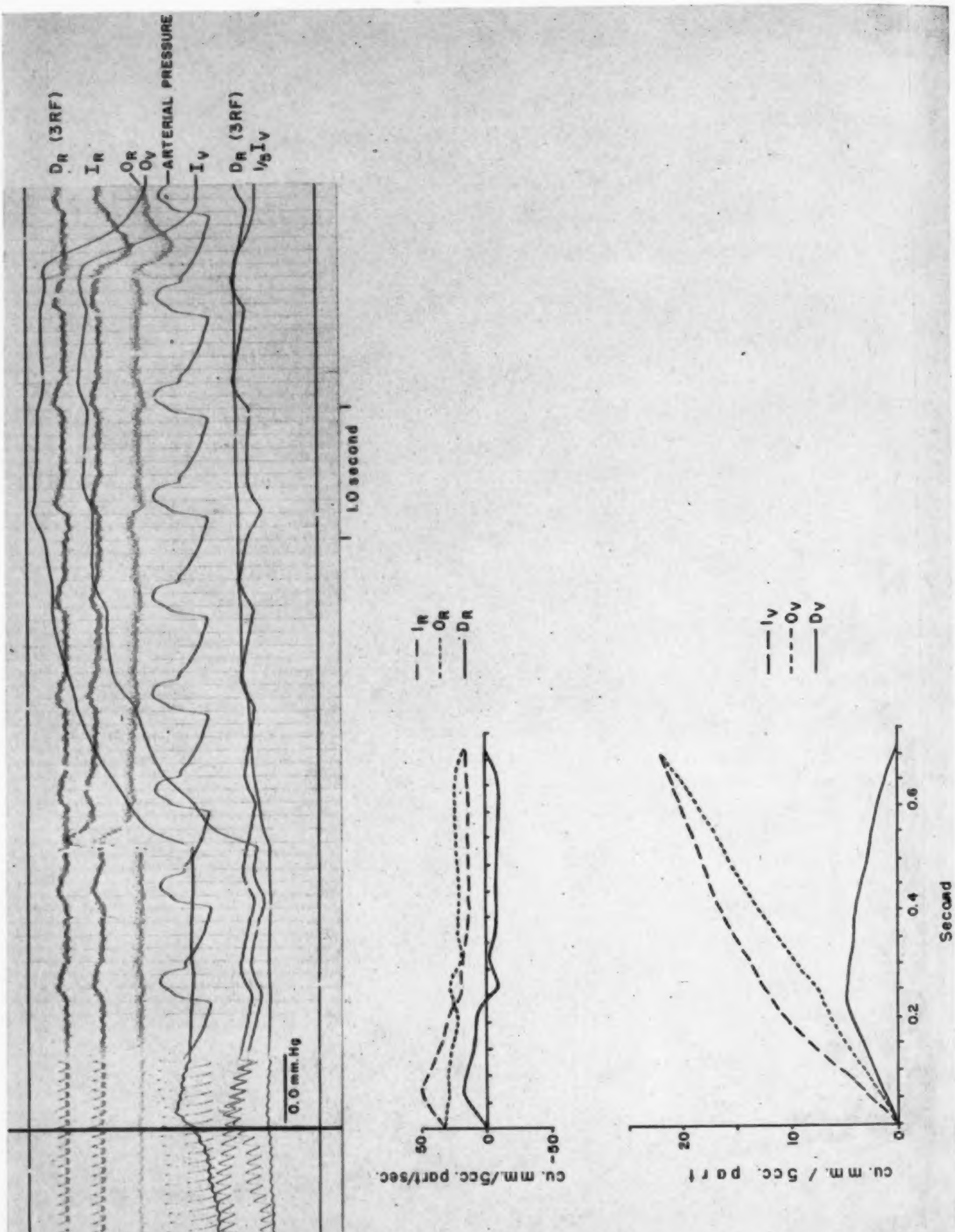

Fig. 1.A. (For legend see opposite page.)

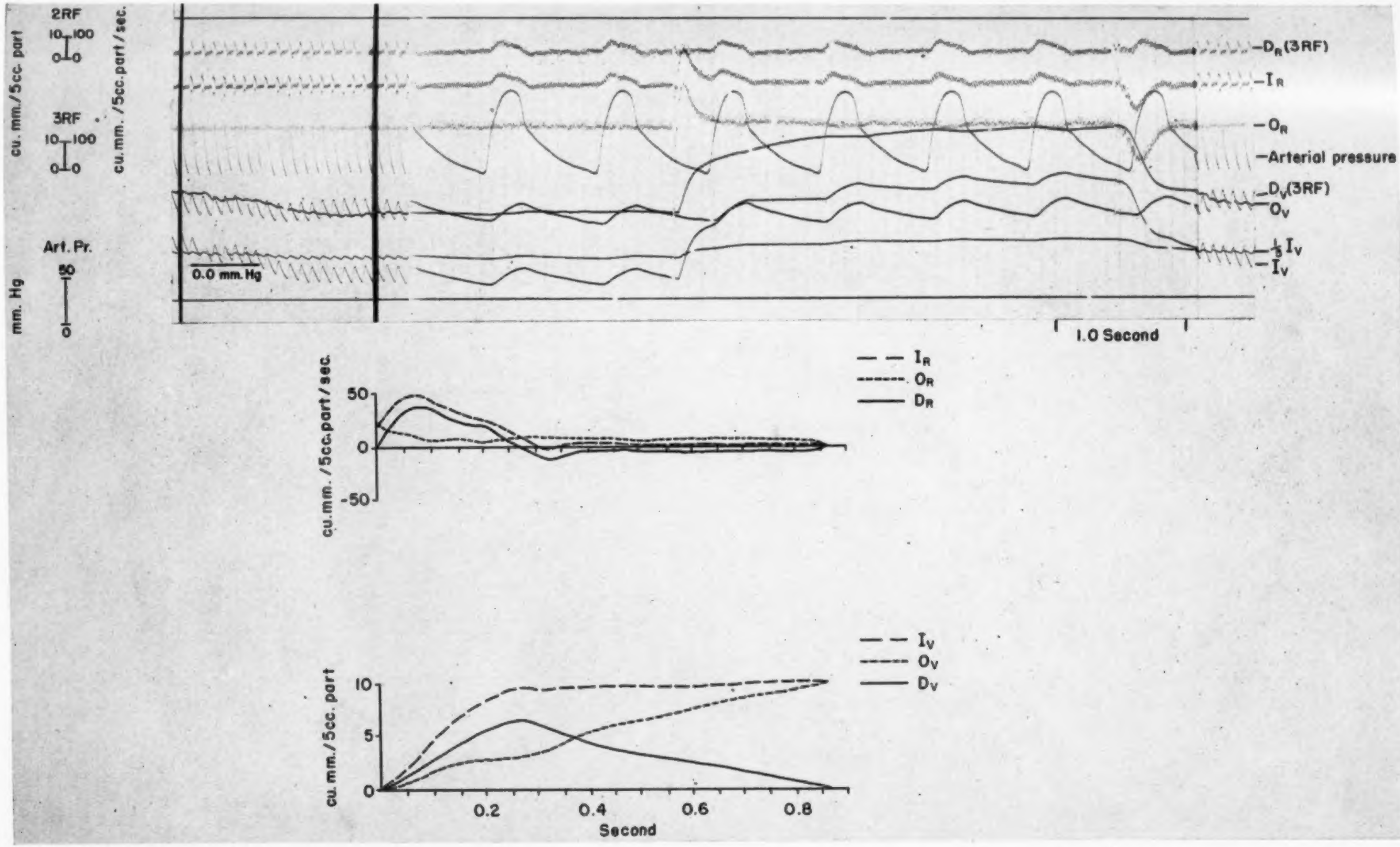

Fig. 1,*B*.

Fig. 1.—Subject No. 5; N. F., 54. Digital rheoplethysmograms with arterial pressure recording (*A*) before and (*B*) after the infusion of norepinephrine. The rapid leveling off of the I_V curve after the administration of norepinephrine indicates a "tight" venous reservoir. All the curves except those labeled *3RF* (third right finger tip) were recorded from the second right finger tip (*2RF*). See text. Blood pressure: 120/73 mm. Hg (*A*) and 190/98 mm. Hg (*B*).

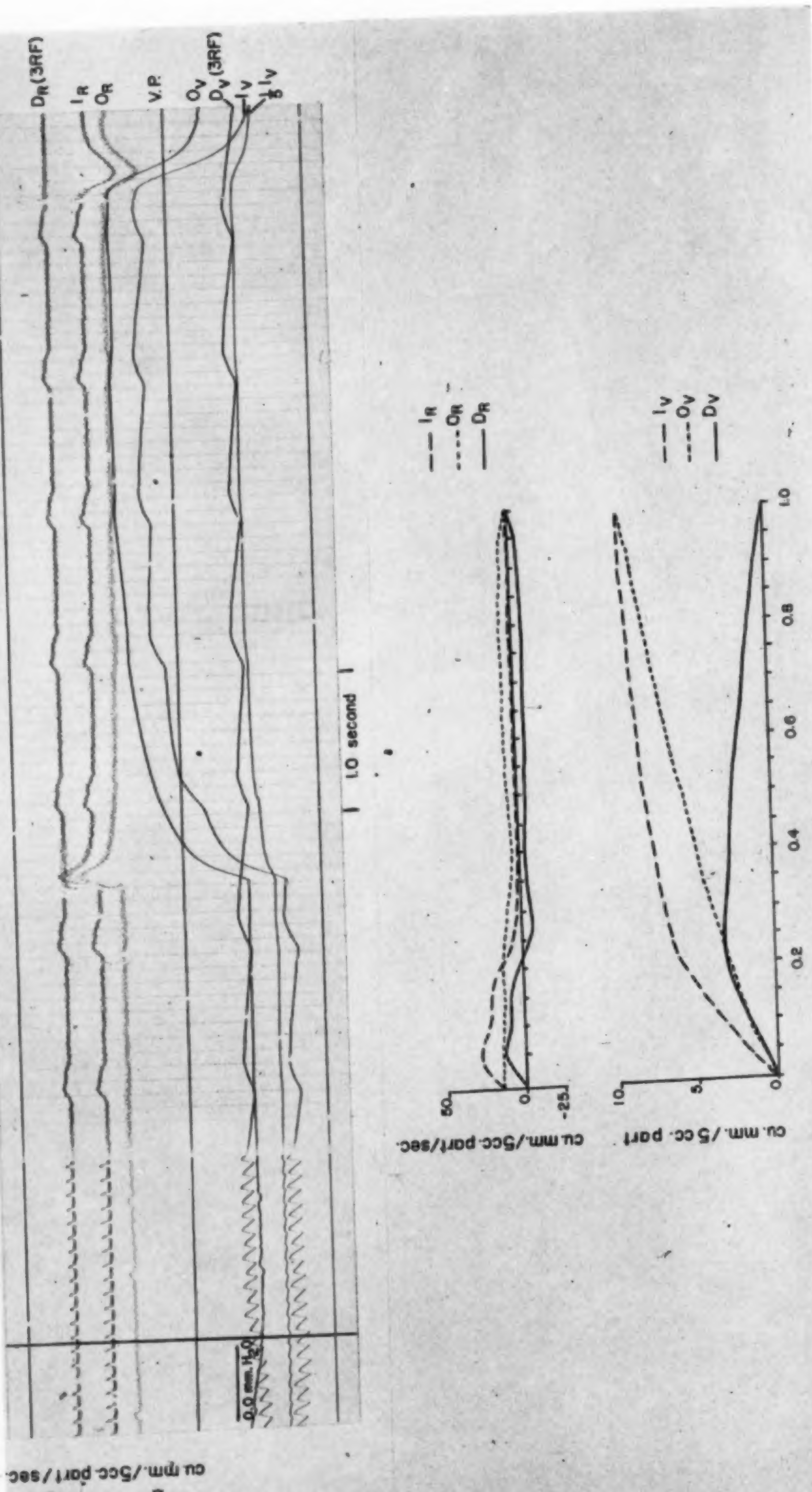

Fig. 2,A. *(For legend see opposite page.)*

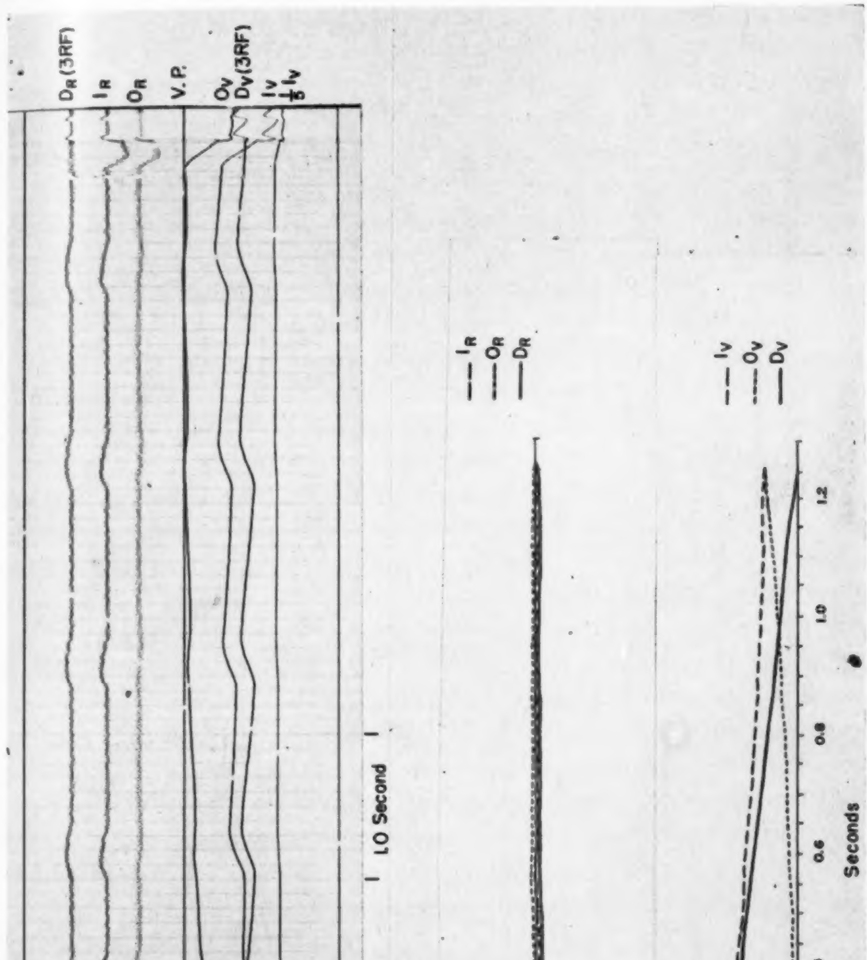

Fig. 2,*B*.

Fig. 2.—Subject No. 1; N. M., 55. Digital rheoplethysmograms with venous pressure recording (*A*) before and (*B*) after infusion of norepinephrine. See text. Blood pressure: 110/70 mm. Hg (*A*) and 220/110 mm. Hg (*B*).

TABLE I. CERTAIN QUANTITATIVE DIGITAL RHEOPLETHYSMOGRAPHIC DATA FOR MAN BEFORE AND AFTER THE ADMINISTRATION OF NOREPINEPHRINE

SUBJECT NUMBER	CYCLE LENGTH (SEC.)		BASAL PULSATILE FLOW (C. MM./5 C.C. PART/SEC.)				MAXIMAL PULSATILE FLOW (C. MM./5 C.C. PART/SEC.)				MEAN RATE OF INFLOW (C. MM./5 C.C. PART/SEC.)								MEAN RATE OF FLOW (C. MM./5 C.C. PART/SEC.)			
											SYSTOLIC				DIASTOLIC							
	BEFORE	AFTER	BEFORE	AFTER	CHANGE	%	BEFORE	AFTER	CHANGE	%	BEFORE	AFTER	CHANGE	%	BEFORE	AFTER	CHANGE	%	BEFORE	AFTER	CHANGE	%
1.	1.08	1.28	15	2	–13	–87	30	19	–11	–37	24.2	13.2	–11.0	–45	3.5	0	–3.5	–100	8.8	1.9	–6.9	–78
2.	0.59	1.10	30	2	–28	–93	45	10	–35	–78	44.0	7.0	–37.0	–84	13.0	2.6	–10.4	–80	22.9	2.6	–20.3	–89
3.	0.84	1.00	30	9	–21	–70	53	28	–25	–47	34.3	17.7	–16.6	–48	5.5	3.2	–2.3	–42	15.8	8.3	–7.5	–47
4.	0.80	0.90	60	17	–43	–72	110	53	–57	–52	57.7	24.8	–32.9	–57	5.7	0	–5.7	–100	28.5	9.4	–19.1	–67
5.	0.70	0.87	42	20	–22	–52	59	48	–11	–19	47.4	29.6	–17.8	–37	21.4	0	–21.4	–100	31.4	11.7	–19.7	–63
6.	1.00	1.15	15	0	–15	–100	98	44	–54	–55	63.1	37.2	–25.9	–41	27.1	12.4	–15.3	–55	36.0	20.9	–15.1	–42
7.	0.79	0.85	24	3	–21	–88	53	23	–20	–38	39.3	14.8	–24.5	–62	14.7	4.3	–10.4	–71	23.4	7.6	–15.8	–68
8.	0.76	0.88	42	10	–32	–76	84	32	–52	–62	44.4	17.6	–26.8	–60	10.0	2.7	–7.3	–73	26.3	8.5	–17.8	–68
9.	0.84	0.86	52	4	–48	–92	72	24	–48	–67	57.6	12.3	–45.3	–79	21.6	7.7	–13.9	–64	35.7	9.5	–26.2	–73
10.	0.60	0.65	20	8	–12	–60	68	49	–19	–28	29.6	10.9	–18.7	–63	9.1	3.0	–6.1	–67	18.3	6.9	–11.4	–62
Mean	0.80	0.95	33	7	–25	–79	67	33	–33	–48	44.2	18.5	–25.6	–58	13.2	3.6	–9.6	–75	24.7	8.7	–15.9	–66

The mean rate of digital flow decreased 66 per cent (range, 42 to 89 per cent). Systolic inflow decreased 58 per cent (range, 37 to 84 per cent), whereas inflow during diastole decreased 75 per cent (range, 42 to 100 per cent). The basal pulsatile flow decreased 79 per cent (range, 52 to 100 per cent), and the maximal pulsatile flow decreased 48 per cent (range, 19 to 78 per cent).[2]

Fig. 1,*A* (Subject No. 5) shows the RPG of a normal subject before the infusion of norepinephrine; the inflow volume (I_V) was 22 c. mm. per 5 c.c. part per pulse cycle. The collecting veins of the digit accumulated blood during both phases of the pulse cycle, indicating a relatively "loose" venous reservoir. The tracings showed the alpha and beta deflections to be well developed.

Fig. 1,*B* is the RPG of the same patient after the infusion of norepinephrine. Total I_V is now 10.2 c. mm. per 5 c.c. part per pulse cycle. All of the accumulation of inflowing blood by the collecting vessels occurred during systole. The "leveling" off of the inflow curve during diastole was probably due to leakage past the occluding cuff, a characteristic of a "tight" venous reservoir. The basal pulsatile flow which is related to diastolic filling was reduced 52 per cent, whereas the maximal pulsatile flow which is related to systolic filling was reduced only 19 per cent. The alpha and beta deflections were reduced in magnitude.

The arterial pressure tracing demonstrated an increase in systolic and diastolic blood pressure. The loss of the dicrotic notch during the infusion of norepinephrine also reflected an increase in peripheral vascular resistance.

Figs. 2,*A* and 2,*B* (Subject No. 1) show essentially the same events for another subject, except that the central venous pressure was recorded simultaneously with the RPG. As can be seen, the venous pressure rose from 108 to 160 mm. H_2O. In a previous study,[4] norepinephrine was also found to increase segmental venous tone in the veins of the forearm of man.

The results for all subjects were essentially the same as those described for Subjects 1 and 5 (Table I).

DISCUSSION

Whereas the action of norepinephrine on the heart, kidneys, lungs, and arterial system of man has been investigated, its effect on the venous system, especially the digital venous system, has been neglected.

As stated previously,[3] the rheoplethysmographic method can be utilized to differentiate pre- and postcapillary vasodilatation and vasoconstriction. It has been indicated that when a descending alpha deflection occurs on a rising beta deflection, there must be precapillary constriction and postcapillary dilatation; and when an ascending alpha deflection exists on a descending beta deflection, there must be precapillary dilatation and simultaneous postcapillary constriction. Since these variations in the alpha and beta deflections are present at all times, they must serve some useful functions. Fluid and electrolyte and other solute exchange, thermal regulation, and the protection of sensitive tactile organs are likely possibilities.

These studies indicate that although norepinephrine is a powerful constrictor of precapillary vessels,[5] the postcapillary vessels are also constricted.

This finding is supported by the demonstration of a "tight" collecting digital venous system with rapid leveling off (Fig. 1,*B*) and occasional falling off (Fig. 2,*B*) of the digital arterial inflow curve (I_V) during inflation of the collecting cuff.

It has been shown rheoplethysmographically that the ringing of a bell or deep inspiration produced precapillary vasoconstriction and a decrease in the volume inflow of blood (I_V) to the finger tip. However, if the collecting cuff is held inflated, filling of the collecting veins will take place over a number of pulse cycles. This is so because the venous reservoir is relatively "loose" and the force (*vis a tergo*) of systolic ejection will eventually force enough blood past the constricted vessels to distend the finger. However, when norepinephrine has been administered, holding the collecting cuff inflated does not result in a rise in the inflow curve (I_V) because the postcapillary vessels and the collecting vessels are so "tight" that they do not accumulate any more blood. In some instances, when the infusion of norepinephrine was stopped while inflation of the collecting cuff was maintained, the volume-time course curve rose relatively suddenly, indicating the moment of relaxation of the collecting reservoirs.

Recently, Rose and Freis[6] demonstrated that norepinephrine increased venous return and right ventricular output. Shadle and associates[7] have furnished evidence that the lung volume of dogs increases during the infusion of norepinephrine. They also found an increase in the volume of the great veins. The shifts in volume occurred after the spleen had been surgically removed. The authors suggested that these shifts were secondary to active constriction of the small peripheral veins and venules. Studies from this laboratory as well as others have shown that norepinephrine increases the central and segmental venous pressure.[7,8] It is probable that norepinephrine constricts the small peripheral veins, such as the veins of the digit, and "squeezes" blood centrally to the right side of the heart and eventually into the lungs. Previously presented theoretical discussions[8] indicate why norepinephrine could result in a shift of blood from vessels of small diameter to those of large diameter, even though it increased smooth muscle tone throughout the entire venous system. Such a course of events could be detrimental to the patient with congestive heart failure.

These studies are important not only because they indicate a mechanism (in addition to direct increase in smooth muscle tone) for the increase in central blood volume and venous pressure observed during the infusion of norepinephrine but also because they demonstrate again a new technique for studying the postcapillary venous system of intact man.

SUMMARY

Norepinephrine decreased the mean rate of digital flow and the basal and maximal rates of pulsatile flow to the digit of man, as recorded rheoplethysmographically. Evidence was also obtained which indicated that the postcapillary vessels as well as the precapillary vessels were constricted by norepinephrine.

It seems likely that norepinephrine "squeezes" blood from the venules and small veins toward the heart and lungs, accounting in part for the increase in

central venous volume and pressure. The tone of the larger vessels is also increased by the drug. These events could be detrimental to the patient in congestive heart failure with high central venous pressure and blood volume.

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Study of Premature Systoles of the Canine Heart by Means of the Spatial Vectorcardiogram

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The electrocardiographic localization of the sites of origin of premature ventricular systoles usually is limited to whether they are simply from a right or left ventricular focus. Although multiple foci from a single ventricle may be observed, the specific site of origin remains obscure. Barker, MacLeod, and Alexander[1] studied electrically induced premature systoles in a young man who required pericardiostomy for suppurative pericarditis. Their studies showed complexes that were of four types: (1) from the most anterior surface of the right ventricle, (2) from the right ventricle in the conus area, (3) from a point high on the anterolateral surface of the left ventricle, and (4) from all other points on the surface of the left ventricle.

Within the past decade several basic concepts regarding the influence of the septal contribution to ventricular activation have materialized.[2-5] One of the aims of the present investigation was to study the changes in the QRSs$\hat{E}$ loop as influenced by the relationship of the septum to the site of origin of premature systoles.

The reference system used in this study was the equilateral tetrahedron. One of the main advantages of this system for our study was that the frontal plane spatial QRSs$\hat{E}$ loop is identical to that determined by the conventional scalar electrocardiogram. Additionally, the normal spatial vectorcardiogram of the dog has been established for the equilateral tetrahedron reference system.[6] It is important to note that there are significant differences between the canine and the human heart with regard to orientation within the body. To interpret the QRSs$\hat{E}$ loop of the dog it is important to visualize the relationship of the canine heart within the body as well as its orientation with regard to the equilateral

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tetrahedron reference system. Fig. 1 shows that the right ventricle lies cephalad* and slightly ventral to the left ventricle. Likewise, the left ventricle lies caudad and slightly dorsal in relation to the right ventricle. The position of the interventricular septum is more complex. As pointed out by Wilson,[7] the interventricular septum is nearly vertical in its dorsal aspect, whereas the ventral part is curved, with its convexity cephalad and to the right. The corresponding ventral surface over the septum is situated in almost a horizontal plane. The average plane of the septum, thus, is neither sagittal nor frontal but midway between the two.

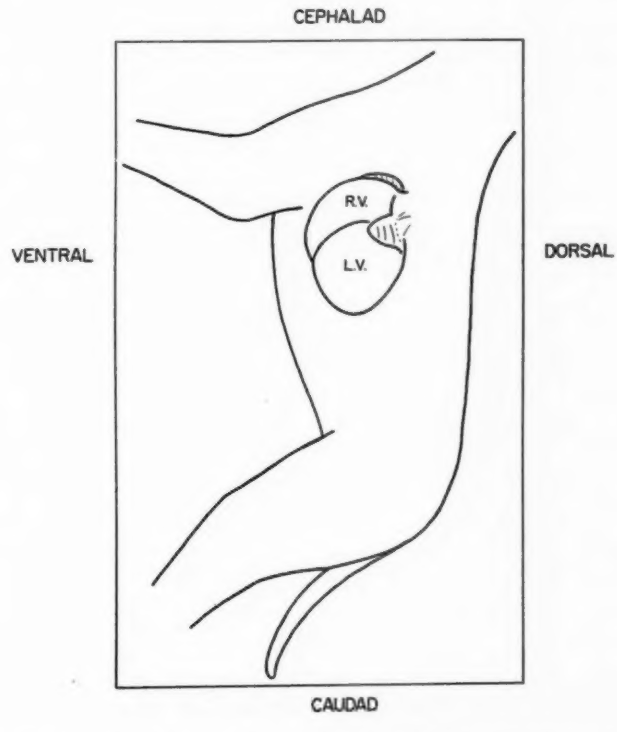


Fig. 1.—Orientation of the canine heart within the body with the animal lying on its right side. This emphasizes that the right ventricle lies cephalad and slightly ventral to the left ventricle.

The orientation of the canine heart with regard to the equilateral tetrahedron is shown in Fig. 2. Depolarization initiated from the right ventricle should proceed through the septum and left ventricle in an inferior direction, with a slightly posterior orientation. Likewise, depolarization proceeding from the left ventricle through the septum and the right ventricular free wall should be directed superiorly, with a slightly anterior orientation.

With the above facts in mind, we undertook the present study of the canine heart, seeking answers to the following questions: (1) Can the sites of origin of premature systoles in the canine heart be localized more specifically than to the

*For the dog, the anatomic relationships will be designated *ventral*, *dorsal*, *cephalad*, and *caudad*. The terms *anterior*, *posterior*, *superior*, *inferior*, and *right* and *left* refer to orientation in the planes of the equilateral tetrahedron reference system.

general areas of the right and left ventricles, and, if so, how many areas can be distinguished? (2) What effect does proximity of the site of origin of premature systoles to the septum have upon the resultant QRSsÊ loop, and what influence can be ascribed to the Purkinje system? (3) Can one explain the findings on the basis of the orientation of the canine right and left ventricles as well as the spatial position of the mean plane of the interventricular septum?

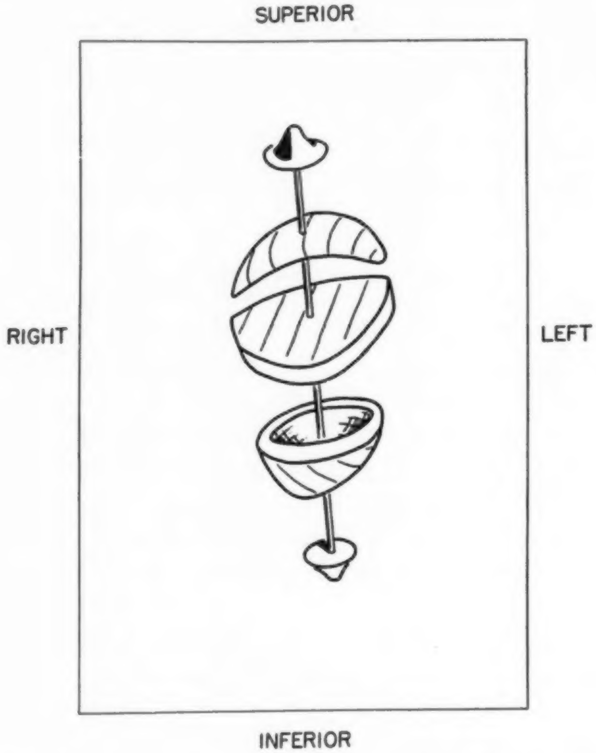


Fig. 2.—Schematic representation of the canine heart, showing its orientation within the equilateral tetrahedron reference system. The positions of the right and left ventricles and their orientation to the *mean* plane of the interventricular septum are shown.

METHOD

Under pentobarbital anesthesia, 15 mongrel dogs which weighed 15 to 25 kilograms were studied in a right lateral decubitus position. Positive pressure respiration was delivered via an endotracheal tube, and the chest was entered through the fourth left intercostal space. Number 32 surgical steel wire, insulated with polyvinyl tubing, was used for the myocardial electrodes. Pairs of electrodes were sutured into the myocardial wall at each locus studied—the electrodes were 2 to 3 mm. apart and penetrated 2 mm. below the epicardial surface. One electrode was used as the stimulating (negative) terminal, and the other electrode served as the neutral (positive) terminal. Previous studies by our group have shown that the placement of the neutral electrode at a distance (e.g., the chest wall) from the stimulating electrode results in deformity of the initial part of the QRSsÊ loop, but with close proximity of the two electrodes no such deformity occurs. A transistor pacemaker developed in our laboratory was used for stimulation, which was carried out at a rate of 150 to 160 per minute with a uniphasic stimulus of 0.5 millisecond's duration. This rate was usually 10 beats per minute faster than the dog's own rate. Measurements of voltage and current were made during the stimulation of at least three different points in each dog—voltage varied from 1.1 to 5 volts, and current varied from 0.8 to 4.0 milliamperes.

To record the VCG and ECG, two sets of electrodes were connected to the dog—one for the ECG (standard limb leads, V_1 and V_6) and the other for the VCG. All recordings were taken with the dog in a right lateral decubitus position and with the thoracotomy wound closed. The equilateral tetrahedron reference system was used with the Sanborn 185 Vector Amplifier and Viso-Scope. The back electrode was a 2 cm. in diameter silver disc placed 2 cm. to the left of the spinous process of the seventh dorsal vertebra.

Records were taken as the heart was stimulated at positions located circumferentially in the basal area, the mid-ventricular area, and near the apex (Fig. 3). Prior to the electrical stimulation of each position, the dog's natural QRSsÊ loop was obtained as a control. If there was any change in over-all configuration or rotation, stimulation was withheld until the control loop had returned to its base-line configuration. In most of the animals, after thoracotomy the frontal plane QRSsÊ loop was of a "figure of eight" or very thin configuration, as noted by Horan, Burch and Cronvich.[8] When the mechanical respirator was used, change in the amplitude of the QRSsÊ loop (as well as the QRS complex of the electrocardiogram) occurred with inspiration, but the loop was constant at the end of expiration. All QRSsÊ loops, therefore, were obtained at the end of expiration. After each VCG was taken, photographs of the heart were made in order to record the exact position stimulated.

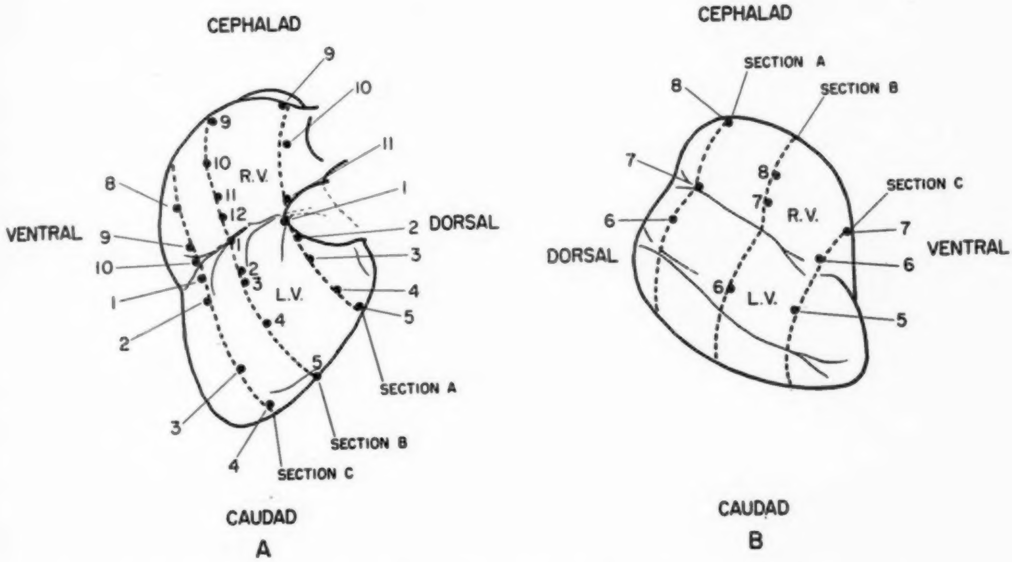


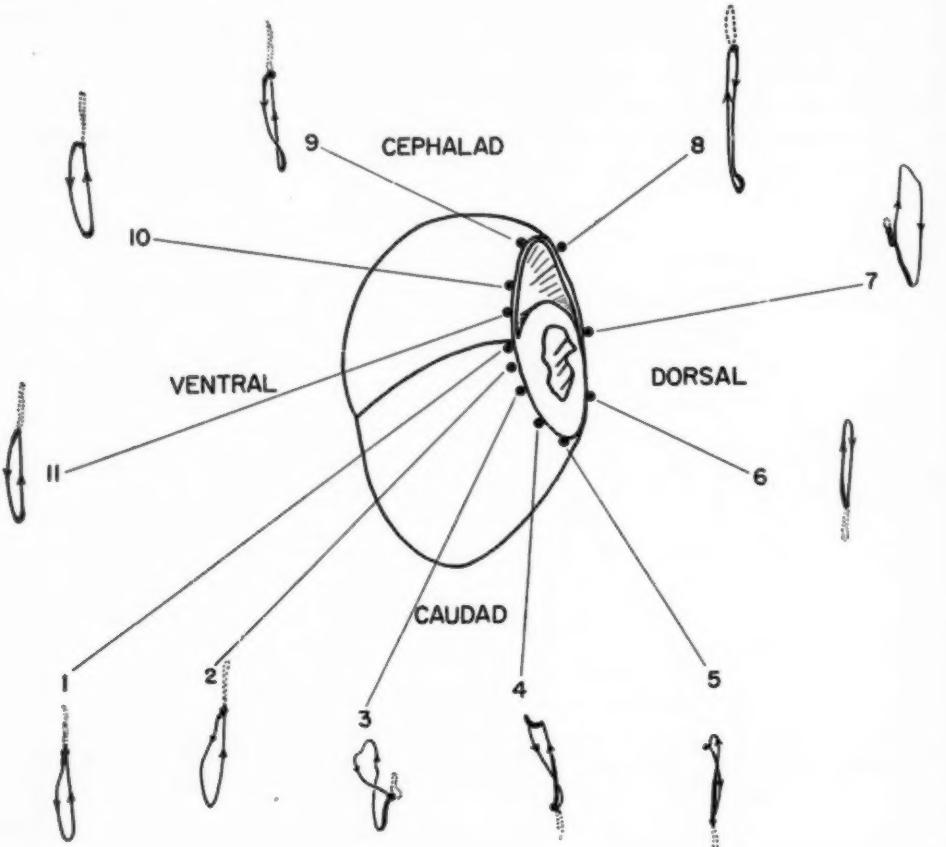
Fig. 3.—Dotted lines indicate the three sections of the heart studied by stimulation of the positions located circumferentially in the basal area, the mid-ventricular area, and near the apex. Diagram *A* depicts the canine heart as viewed through a left anterior thoracotomy incision with the dog lying on its right side. Diagram *B* shows the three sections studied over the dorsal surface.

As a control on variability between different dogs, three similar points over each ventricle were stimulated first in each dog (Fig. 3: Positions 4 and 10 of Section A and B; Positions 3 and 8 of Section C). The resultant QRSsÊ loops for each position were similar in all animals as to direction of QRSsÊ-loop rotation, areas of slowing, and QRS axis position; however, variations in shape occurred at the apex of the QRSsÊ loops (looping, pointing, and flattening).

At the end of each experiment the endocardium was stained with Lugol's solution[9] in order to demonstrate the conduction system, which was grossly normal in all animals. In the right ventricle of all dogs the main bundle was intact and the Purkinje fibers ramified normally over the endocardial surface, with some false tendons spanning the ventricular cavity. In the pulmonary conus area the Purkinje tissue was very sparse. In the left ventricle, both anterior and posterior branches of the left bundle were intact. There were ramifications over the left ventricular endocardium, and the false tendons were more prominent than in the right ventricle.

RESULTS

With each stimulation, QRSsÊ loops were recorded in the frontal, right sagittal, and superior planes. Only the results recorded in the frontal plane will be presented. In some instances the sagittal and superior planes showed changes not evident in the frontal plane—these will be mentioned where appropriate. Figs. 4, 5, and 6 show representative QRSsÊ loops of sites stimulated in the three sections of the heart.



SECTION A

Fig. 4.—Section A: Basal Area. The QRSsÊ loops of premature systoles produced by stimulation at the points indicated. Thickened areas represent obvious slowing of the QRSsÊ loop. Positions *4, 5, 6, 8, 9, 10,* and *11* are over the free walls. The other positions (*1, 2, 3,* and *7*) are adjacent to the septum. The diagram of the heart is presented to emphasize the relative positions of the canine right and left ventricles anatomically (ventral, dorsal, caudad, and cephalad). The orientation of the QRSsÊ loops is as noted for the frontal plane in Fig. 2.

The findings are presented with reference to stimulation of the following areas: the right ventricular free wall, left ventricular free wall, and the ventral and dorsal areas adjacent to the interventricular septum.

1. *Right Ventricular Free Wall (Total Positions Stimulated: 50).*—In all areas stimulated the orientation of the QRSsÊ loop was directed inferiorly and

slightly posteriorly. There was very slight slowing of the initial forces. This contrasts to the marked slowing when the left ventricular free wall was stimulated.

There was a consistent relationship of the direction of rotation of the QRSsÊ loop in the frontal plane for stimulation of the ventral versus the dorsal free wall. In all three sections, ventral positions gave QRSsÊ loops with counterclockwise rotation in the frontal plane. The reverse rotation (clockwise) occurred for the dorsal surface. For points stimulated over the free wall, which were difficult to judge as to a definite ventral or dorsal position, the QRSsÊ loops were of the type foı either the ventral or dorsal free wall, with no consistency for either type noted.

Stimulation of points equidistant from the septum on the ventral wall gave no change in the frontal plane as to the axis or direction of rotation of the

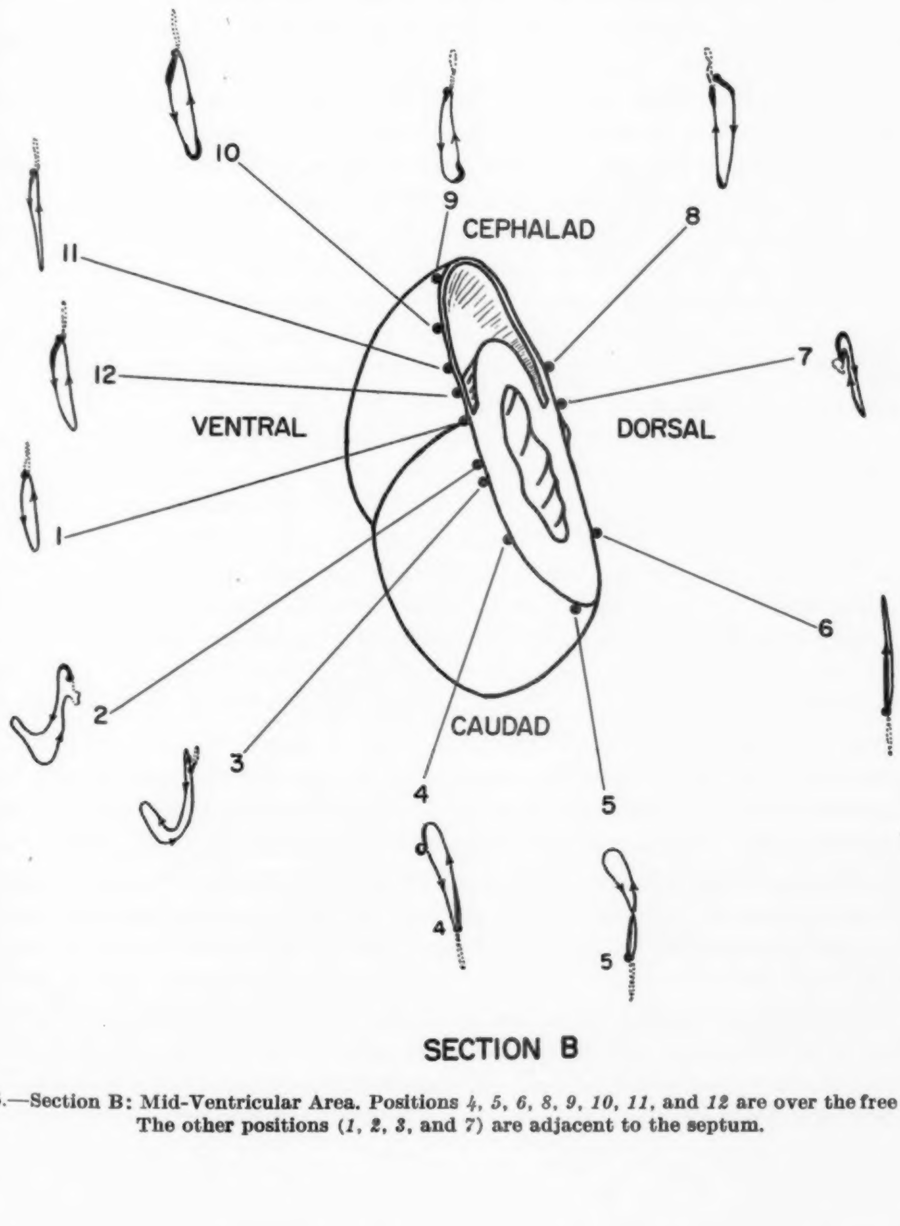


Fig. 5.—Section B: Mid-Ventricular Area. Positions *4, 5, 6, 8, 9, 10, 11,* and *12* are over the free walls. The other positions (*1, 2, 3,* and *7*) are adjacent to the septum.

QRSsÊ loop (e.g., Fig. 3: Position 11 of Section A, Position 12 of Section B, and Position 9 of Section C). Similar findings were noted for the dorsal surface.

2. *Left Ventricular Free Wall* (*Total Positions Stimulated: 48*).—All QRSsÊ loops were directly superior and slightly anterior. In all areas there was marked slowing of the initial forces of the loop.

As was present over the right ventricle, there was a consistent direction of rotation of the QRSsÊ loop for stimulation of the ventral versus the dorsal free wall. In ventral and dorsal positions the initial portion of the QRSsÊ loop in the frontal plane was almost straight superiorly—at the apex of the loop there was a counterclockwise rotation for ventral positions, with a clockwise rotation for dorsal areas. As noted over the right ventricle, points which were situated either slightly ventral or dorsal gave loops of either a ventral or dorsal type. Also, stimulation of positions equidistant from the septum showed no change in axis or direction of rotation of the QRSsÊ loops as the points of stimulation were shifted from base to apex.

3. *Areas of the Right and Left Ventricles Adjacent to the Interventricular Septum.*—The ventral longitudinal groove with the descending coronary vessels overlies the septum ventrally in the canine heart. Dorsally the less distinct dorsal longitudinal groove with a descending branch from the right coronary artery is the external landmark of the septum. In the three sections of the heart studied, there was a transitional zone near the interventricular septum where the QRSsÊ loops obtained were not of the type observed by stimulation of the free wall of either the left ventricle or the right ventricle (Figs. 4, 5, and 6). Stimulation subepicardially of areas adjacent to the longitudinal grooves (interventricular septum) gave the findings described below.

a. *Left ventricle adjacent to ventral longitudinal groove* (*total positions stimulated: 25*)*:* As one moves from the free wall of the left ventricle toward the coronary vessels, there is a transitional area of 0.5 to 2.0 cm. (depending on the size of the heart) where the QRSsÊ loops are directed mostly inferior but are quite different from those obtained over the free wall of either ventricle. By moving the position stimulated from the free wall toward the septum, transitional QRSsÊ loops could be obtained which changed from almost typical left ventricular type of QRSsÊ loops (Position 3 of Section A) to an intermediate type (Positions 2 and 3 of Section B), to an almost typical right ventricular type of QRSsÊ loop (Position 1 of Section A). In the stimulation of all points immediately to the left of the coronary vessels (Position 1 of Section A) the QRSsÊ loops in the frontal plane were similar in axis and direction of rotation to those obtained in the stimulation of the ventral surface of the free wall of the right ventricle.

In 3 dogs the following was observed as the point of stimulation moved from left to right across the septum in Section B: As the stimulation point moved across the septum, the QRSsÊ loops in the frontal plane were all of the type obtained over the adjacent free wall of the right ventricle; however, the sagittal and superior planes revealed that the orientation changed in an anterior to posterior direction. As the point shifted from the left side of the coronary vessels to the mid-septum, in between the vessels, the loop shifted in a posterior direction—this shift continued even further posteriorly for points on the right side of the vessels.

b. *Right ventricle immediately adjacent to the ventral longitudinal groove* (*total positions stimulated: 18*): All positions stimulated in this area gave QRSsÊ loops typical for the ventral surface of the free wall of the right ventricle, with the loop directed inferiorly and posteriorly (Position 12 of Section B).

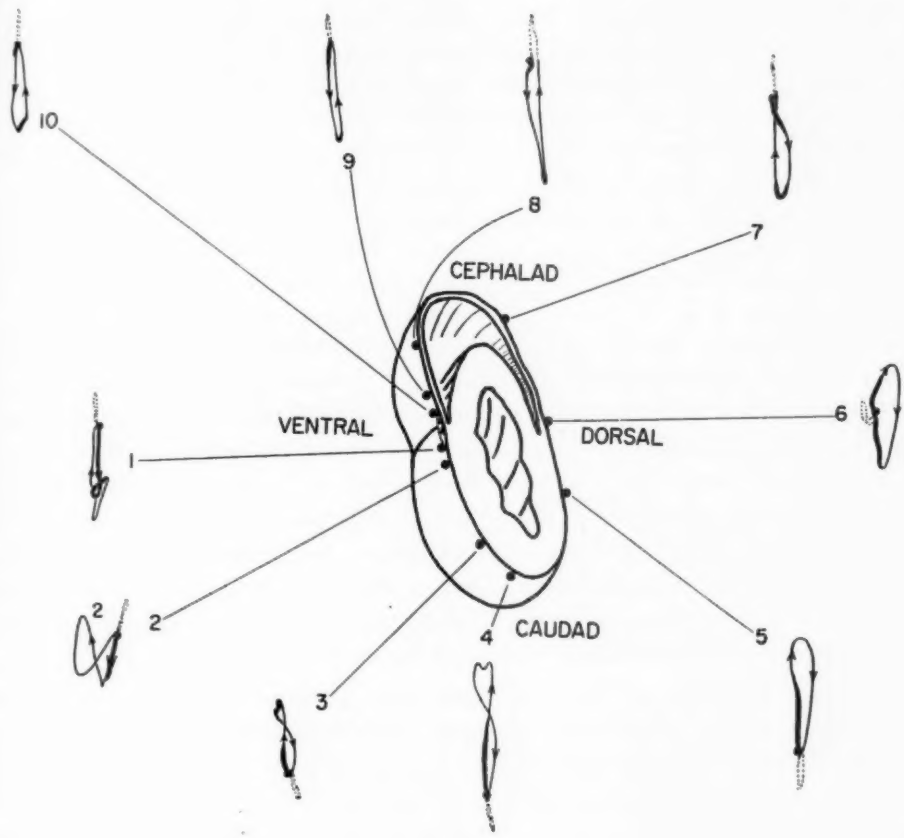


Fig. 6.—Section C: Apical Area. Positions *3, 4, 5, 7, 8,* and *9* are over the free wall. The other positions (*1, 2, 6,* and *10*) are adjacent to the septum

c. *Right ventricle adjacent to the dorsal longitudinal groove* (*total positions stimulated: 15*): The QRSsÊ loops from points stimulated in this area were, in general, the opposite of those obtained from the ventral surface of the left ventricle adjacent to the coronary vessels. This area varied from 0.5 to 1.5 cm. to the right of the dorsal longitudinal groove. As the stimulation point approached the septum from the right in this transitional area, the QRSsÊ loop changed from a type resembling that from the dorsal free wall of the right ventricle (Position 7 of Section B) to an intermediate type (Position 6 of Section C), and then to a type with more similarities to those obtained over the left ventricular free wall (Position 7 of Section A). The rotation of the loop in the frontal plane was in a clockwise direction, with the initial forces oriented superiorly.

d. *Left ventricle adjacent to the dorsal longitudinal groove (total positions stimulated: 12):* In the frontal plane, QRSsÊ loops of premature systoles from this area were identical to those from the dorsal surface of the free wall of the left ventricle.

4. *Review of Scalar Electrocardiograms.*—Only frontal plane QRSsÊ loops have been discussed. Although the electrocardiograms were reviewed, the QRS loops derived from these are not presented since they are identical to the frontal plane QRSsÊ loops of the equilateral tetrahedron reference system. However, measurement of the QRS intervals revealed: (1) dog's natural QRS duration, 0.04 to 0.05 second; (2) right ventricular free wall premature systoles, 0.07 to 0.08 second; (3) left ventricular free wall premature systoles, 0.08 to 0.09 second; (4) ventral and dorsal transitional zone premature systoles, 0.05 to 0.07 second.

DISCUSSION

No quantitative analysis of the QRSsÊ loops was made because of the acute type of experimental conditions with some air remaining in the chest. However, the same relative conditions were present in all dogs, and a qualitative analysis is valid. Results were consistent in all dogs except for occasional variations in the transitional areas, especially near the apex. Such variations occurred primarily in the sagittal and superior planes. Also, displacement of the heart produced marked variations in the resultant QRSsÊ loops. As mentioned, all stimulations were carried out only after the dog's natural QRSsÊ loop returned to its base-line configuration. The effect of displacement of the heart upon premature systole complexes has been studied by Katz and Ackerman.[10]

Localization of Sites of Origin of Premature Systoles.—Since the classic work of Sir Thomas Lewis[11] and of Rothberger and Winterberg,[12] little has appeared in the literature concerning the graphic registration of electrical events of premature ventricular systoles in the canine heart. These original studies of the canine heart were done with two to three bipolar leads of the electrocardiogram. Lewis[11] studied the ventral surface of the canine heart. He noted that as the site of stimulation shifted from the right ventricle across the descending branch of the left coronary artery, the QRS complex changed abruptly to an intermediate type, different from complexes obtained with stimulation of the left ventricular free wall. Our results are consistent with Lewis' studies[11] of the ventral surface of the canine heart. In addition, we were able to demonstrate that the QRSsÊ loops of premature systoles originating in the subepicardial region of the canine heart allow identification of the site of origin into six areas: ventral and dorsal right ventricular free wall, ventral and dorsal left ventricular free wall, ventral transitional area of the left ventricle adjacent to the septum, and dorsal transitional area of the right ventricle in proximity to the septum. Also confirmed vectorcardiographically is Lewis' finding of the similarity of ECG curves from the stimulation of points equidistant from the septum over the ventral surface, though varying in position between the base and apex; in our studies, this similarity also was present over the dorsal surface.

Influence of Proximity of Site of Origin to the Interventricular Septum and Role of Purkinje System.—The importance of the proximity of subepicardial positions to the interventricular septum is shown. The transitional zone ventrally is along the left side of the coronary vessels (i.e., over the left ventricle), whereas dorsally this area is over the right ventricle. Lewis[11] pointed out that the transitional curves were probably due to almost simultaneous involvement of the right and left ventricular Purkinje systems. Our results differ slightly from those of Lewis with regard to the frontal plane—stimulation of points immediately on the left side of the ventral descending coronary vessels gave QRSsÊ loops typical of those of the right ventricular wall. Also, stimulation of points immediately on the right ventricular side of the dorsal longitudinal groove gave loops in the frontal plane similar to those of the left ventricular free wall. This difference from Lewis' findings may be related to our placement of electrodes 1 to 2 mm. below the epicardial surface. By measurement from the point of stimulation to the stained Purkinje system in 2 dogs, it could be shown that when right ventricular type of QRSsÊ loops were obtained from points stimulated on the left side of the ventral longitudinal groove, the point stimulated was closer to the right ventricular Purkinje system than to the left. For example, in Position 1 of Section A the point of stimulation was 7.0 mm. distant from the right Purkinje tissue and 9.5 from the left.

The role of the Purkinje system, therefore, becomes of extreme importance in determining the QRSsÊ loop of premature systoles arising in the transitional zones noted. The configuration of the complex is influenced largely by the relative distance of the focus from the two Purkinje networks. Thus, premature systoles arising in the morphologic left ventricular mass may resemble a left, right, or transitional premature systole.

The consistent slowing of the initial forces noted from areas stimulated over the left ventricle as compared to the right ventricle can be attributed to the large muscle mass situated between the stimulating electrode and the Purkinje system, as well as the progression of the wave front to the larger left ventricular mass as compared to the smaller right ventricular mass.[11] In the sections studied, the distance from the stimulating electrode to the Purkinje tissue approximated the thickness of the left ventricular free wall in the case of all points which yielded QRSsÊ loops with marked slowing of the initial forces. That the initial slowing of forces is influenced by factors other than the distance between the electrode and the Purkinje tissue was demonstrated by stimulating the apex of the left ventricle (the thinnest area of the left ventricular wall). Here the QRSsÊ loop showed the type of slowing of the initial forces obtained over the rest of the free wall of the left ventricle.

Relationship of the Heart to the Reference System.—The canine heart presents an excellent situation for the study of the QRSsÊ loops of premature ventricular systoles. The resultant QRSsÊ loops of points stimulated over the free wall of the left ventricle (lying caudad and dorsal in reference to the interventricular septum and right ventricle) were oriented in a superior and slightly anterior direction. The resultant QRSsÊ loops from points over the free wall of the right ventricle were in the opposite direction, i.e., in an inferior and posterior direction.

These results are best explained by the orientation of the canine right and left ventricles and the spatial position of the mean plane of the interventricular septum as shown in Fig. 2. A similar type of mean QRS axis in complete bundle branch block has been discussed by Wilson[7] in relationship to the position of the interventricular septum and the ventricular walls in the canine as compared to the human heart.

One cannot apply specific findings in the canine heart to the human heart because of many differences between the two. For example, the orientation of the canine heart within the reference system is much different from that of the human heart. Also, this study has been done in normal dogs with absence of hypertrophy of either ventricle, and only subepicardial points were stimulated. However, many studies[13-15] over the past few years in the canine heart have contributed greatly to a better understanding of electrophysiologic phenomenon occurring in the human heart. It is hoped that this study of the canine heart may stimulate interest which will lead to a better understanding of the genesis of the electrocardiographic findings in premature systoles in the human heart.

SUMMARY

Vectorcardiographic recordings of premature systoles arising in the subepicardial region of the canine heart were studied. Review of the QRSsÊ loops of premature systoles originating in the subepicardial area of the canine heart allows identification of the site of origin into six areas: ventral and dorsal right ventricular free wall, ventral and dorsal left ventricular free wall, ventral transitional area of the left ventricle adjacent to the septum, and dorsal transitional area of the right ventricle in proximity to the septum.

The QRSsÊ loops were characteristic for each of the ventricular free walls and showed consistent differences between ventral and dorsal positions. Transitional QRSsÊ loops were obtained from stimulation of areas proximal to the septum. The transitional area was over the left ventricle ventrally and over the right ventricle dorsally. Transitional loops were obtained from points almost equidistant from the left and right Purkinje systems, as noted by Lewis in electrocardiographic studies.[11]

In the frontal plane, QRSsÊ loops similar to those over the right ventricle could be obtained on the left side of the descending coronary vessels ventrally; also, curves similar to those from the left ventricle were obtained on the right side of the septum dorsally. The resultant QRSsÊ loops from the free ventricular walls are best explained by the orientation within the reference system of the canine right and left ventricles and the spatial position of the mean plane of the interventricular septum.

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The Effect of Diphenylhydantoin (Dilantin) Sodium on Atrial Flutter and Fibrillation Provoked by Focal Application of Aconitine or Delphinine

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Atrial fibrillation and flutter due to focal application of aconitine can be stopped at once by cooling the area treated; however, the response of aconitine-induced extrasystoles to systemic agents, such as quinidine,[15] which usually abolish arrhythmias is poor. When aconitine is given intravenously, the resulting extrasystoles can be abolished by inhalation of oxygen with 20 per cent carbon dioxide,[11] whereas hypercapnia has no influence on the fibrillation caused by the topical application of aconitine.[13] The difference in the intensity of the stimulus has been considered as a possible explanation.

Because the heart and the central nervous system respond to drugs in a similar manner, and the convulsive seizures seen after cerebral trauma and scar formation may be compared to the attacks of ventricular tachycardia following myocardial infarction, Harris and Kokernot[5] investigated the effect of diphenylhydantoin sodium (Dilantin) on ventricular tachycardias induced in dogs by ligation of the coronary arteries. The present study is concerned with the effect of diphenylhydantoin sodium on the atrial and ventricular arrhythmias caused by the focal application of aconitine or delphinine to the heart.

METHOD

Crystalline aconitine or delphinine was used in all experiments. The dogs were anesthetized with Nembutal (18 mg. per kilogram of body weight) and morphine (8 mg. per kilogram). Artificial respiration was instituted and the heart was exposed. Morphine was added to Nembutal in order to increase the vagus tonus. This leads to slowing of the heart and facilitates the appearance of ectopic arrhythmias. The vagi were not severed, in order to avoid a sinus tachycardia, and a shielded electrode was applied to the right vagus in the neck. A few crystals of aconitine or delphinine were applied to the surface of the right atrium in the appendix area near the head of the sinus node. Whereas with focal application of aconitine it is not possible to predict whether flutter or fibrillation will appear, delphinine always leads to flutter.[14] The arrhythmia appeared in about 1 minute with aconitine, and between 2 to 3 minutes with delphinine.

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The diphenylhydantoin used was a freshly prepared solution and was injected into the jugular vein. The dose amounted to 5 mg. per kilogram of body weight. The electrocardiogram was registered in Lead II. Fourteen experiments were performed with aconitine and 8 with delphinine.

RESULTS

In all of the experiments with aconitine and in 6 out of the 8 experiments with delphinine the arrhythmia (flutter or fibrillation) was stopped abruptly and soon after the injection. In the other 2 experiments with delphinine the atrial rate gradually decreased and sinus rhythm appeared.

In most of the experiments the arrhythmia disappeared within 2 minutes. In one instance an aconitine-induced fibrillation was replaced by sinus rhythm in 10 seconds. These intervals varied within the same experiment; thus, in one experiment, fibrillation caused by aconitine was stopped 2 minutes and 6 seconds after the first injection, whereas 24 minutes later the same dose of diphenylhydantoin abolished the fibrillation after only 12 seconds. In other experiments the second injection acted after an interval longer than that after the first.

In all experiments the flutter or fibrillation returned after a variable interval. The length of time varied between 2 minutes and 10 seconds and 14 minutes. Heating of the focus of application (Fig. 1) or slight stretching or pressure exerted with a probe on the focus (Fig. 1) caused the reappearance of the arrhythmia.

In all experiments the spontaneous return of the flutter or fibrillation was preceded by extrasystoles. At first, only occasional extrasystoles appeared, but soon a bigeminal rhythm prevailed and was followed by groups of trigeminal rhythm, multiple extrasystoles, and, finally, flutter or fibrillation. This is of interest because at the onset and termination of these arrhythmias induced by focal aconitine or delphinine without diphenylhydantoin no extrasystoles were observed.

In 7 experiments an A-V rhythm appeared (Figs. 4 and 6) after diphenylhydantoin, and in one experiment there was an interference-dissociation (Fig. 5), with the A-V rate faster than the sinus rate and no reversed conduction from the A-V node to the atria.

Both aconitine and delphinine increase the vagal tone. It may be so marked with aconitine that complete standstill of the atria occurs; this can be abolished by atropine.[10] Paralysis of the vagus after injections of delphinine has been described but was not seen in these experiments, probably because of the small amounts of the drug, which are absorbed when the substance is applied focally. Paralysis of some of the branches of the vagus may account for the unusual effect seen in Figs. 3, 4, and 5 and observed frequently: The influence of vagus stimulation on the formation of atrial impulses is almost absent while the A-V conduction is normally inhibited. The coupling of the extrasystoles occasionally is prolonged during vagal stimulation. Thus it increases in Fig. 3 from 0.18 to 0.20 second.

The RS-T segments and the T waves show characteristic and progressive changes when toxic doses of diphenylhydantoin are injected.[12] In the present experiments, with the smaller doses employed, the T waves became higher or lower: positive T waves became negative and vice versa, as Figs. 1 through 6 show. No definite rules were discovered.

Fig. 1.—Experiment of Dec. 2, 1958. The beginning of *A* shows atrial fibrillation which appeared after focal application of aconitine crystals to the sinus node area of the right atrium. An intravenous injection of diphenylhydantoin was given. Sinus rhythm reappeared after 96 seconds (middle of *A*). *B* shows a bigeminal rhythm caused by atrial extrasystoles which appeared during the warming of the area to which aconitine had been applied. The warming was performed 4 minutes after the injection and began at the level of the fourth beat (*B*). Two minutes later, atrial fibrillation reappeared and a second injection of diphenylhydantoin led to sinus rhythm within 58 seconds (*C*). Rewarming the focus of application 3 minutes and 15 seconds later provoked atrial extrasystoles (*D*). The warming started at the eighth complex. Touching the area of application lightly with a probe led to fibrillation (*E*). A third injection of diphenylhydantoin 5 minutes and 36 seconds after the second one caused sinus rhythm with atrial bigeminal rhythms. The transition into sinus rhythm is seen in the first part of *F*. The second part of *F* again shows atrial bigeminy, which appeared 7 minutes after the third injection of diphenylhydantoin. There is no prolongation of the P-R intervals and no widening of the QRS complexes in spite of the three injections of diphenylhydantoin within a relatively short time.

Fig. 2.—Experiment of Dec. 9, 1958. Aconitine, applied to the area of the head of the sinus node, provoked atrial flutter which changed into sinus rhythm after the injection of diphenylhydantoin (*A*). The change occurred 10 seconds after the injection. *B* was obtained 3 minutes and 40 seconds later. During vagal stimulation (beginning of *B*) a 2:1 block is seen with regular atrial activity; after the end of the stimulation, atrial bigeminy appeared. This soon changed into a trigeminal rhythm (*C*). A second injection of half the dose of diphenylhydantoin had led to bigeminal rhythm, and the coupling was prolonged from 0.20 to 0.24 second; the T waves are lower (first part of *D*). A reinjection of the same half-dose of diphenylhydantoin changed the bigeminal rhythm into sinus rhythm (second part of *D*). *E* was obtained 6 minutes and 40 seconds after the first injection and shows multiple (3-4) extrasystoles. Nineteen seconds after a renewed injection of diphenylhydantoin the coupling of the extrasystoles becomes longer (*F*) and they finally disappear. The T waves become flat and the RS-T segments are depressed. Two minutes and 30 seconds after the last injection, and 19 minutes after the first one, an atrial bigeminal rhythm is again present (*G*). Twenty-five minutes and 20 seconds after the first injection an atrial tachycardia appears (*H*), and is transformed by a new injection of diphenylhydantoin into a sinus rhythm. The T waves are higher. Again the P-R interval is prolonged from 0.07 (in *A*) to 0.09 second. There is no change in the QRS complexes.

Fig. 3.—Experiment of Feb. 17, 1959. *A* shows atrial flutter caused by focal application of delphinine to the area of the sinus node. The flutter waves show an increase in rate of from 400 to 500 during vagal stimulation. An injection of diphenylhydantoin converts this flutter to sinus rhythm in 16 seconds. The transition is seen in *B*. The appearance of a temporary A-V rhythm is also noted in *B*. Atrial extrasystoles appeared 5 minutes and 10 seconds after the conversion to sinus rhythm (*C*). Stimulation of the vagus influenced the atrial rate and rhythm little, but caused A-V block. The coupling increased from 0.18 to 0.20 second. *D* shows the end of a vagal stimulation 2 minutes later, and *E* and *F* were obtained during vagal stimulation and atrial bigeminy 7 minutes later. Finally, atrial flutter appeared (*G*), and was transformed into A-V rhythm by a second injection of diphenylhydantoin.

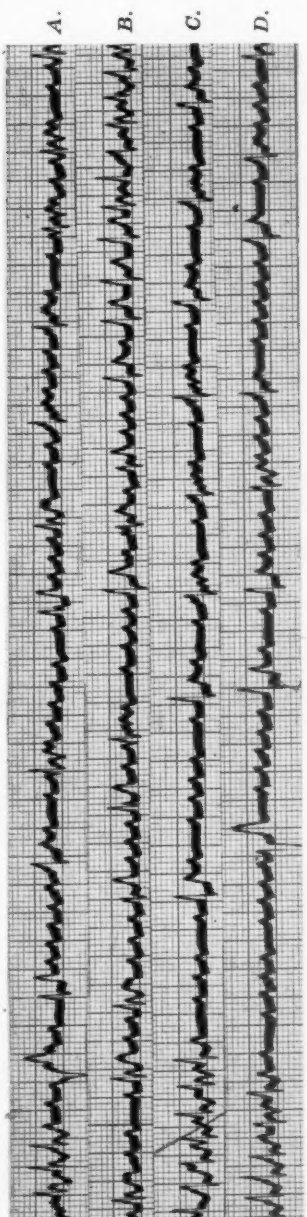

Fig. 4.—Experiment of June 9, 1959. The tracings of *A* and *B* are continuous. Atrial flutter had appeared after focal application of aconitine to the usual area. An intravenous injection of diphenylhydantoin, given 8 minutes and 34 seconds before, had caused sinus rhythm, but the flutter reappeared. During vagal stimulation an A-V block permits the study of the atrial rhythm (*A* and *B*). The form of the flutter waves remains unchanged, but pauses appear which are twice the length of a normal P-P interval. A second and third vagal stimulation (*C* and *D*) show the same result.

Fig. 5.—Experiment of Nov. 18, 1959. Aconitine which was applied as previously caused atrial flutter. Vagal stimulation increased the rate in the usual manner (*A*). The injection of diphenylhydantoin caused a series of atrial extrasystoles (*B*), and finally sinus rhythm (*C*). A few seconds later, dissociation with interference appeared (*D*). Six and one-half minutes later, atrial bigeminy was present (*E*). Vagal stimulation inhibited the A-V conduction, but influenced the atrial arrhythmia little (*E* and *F*).

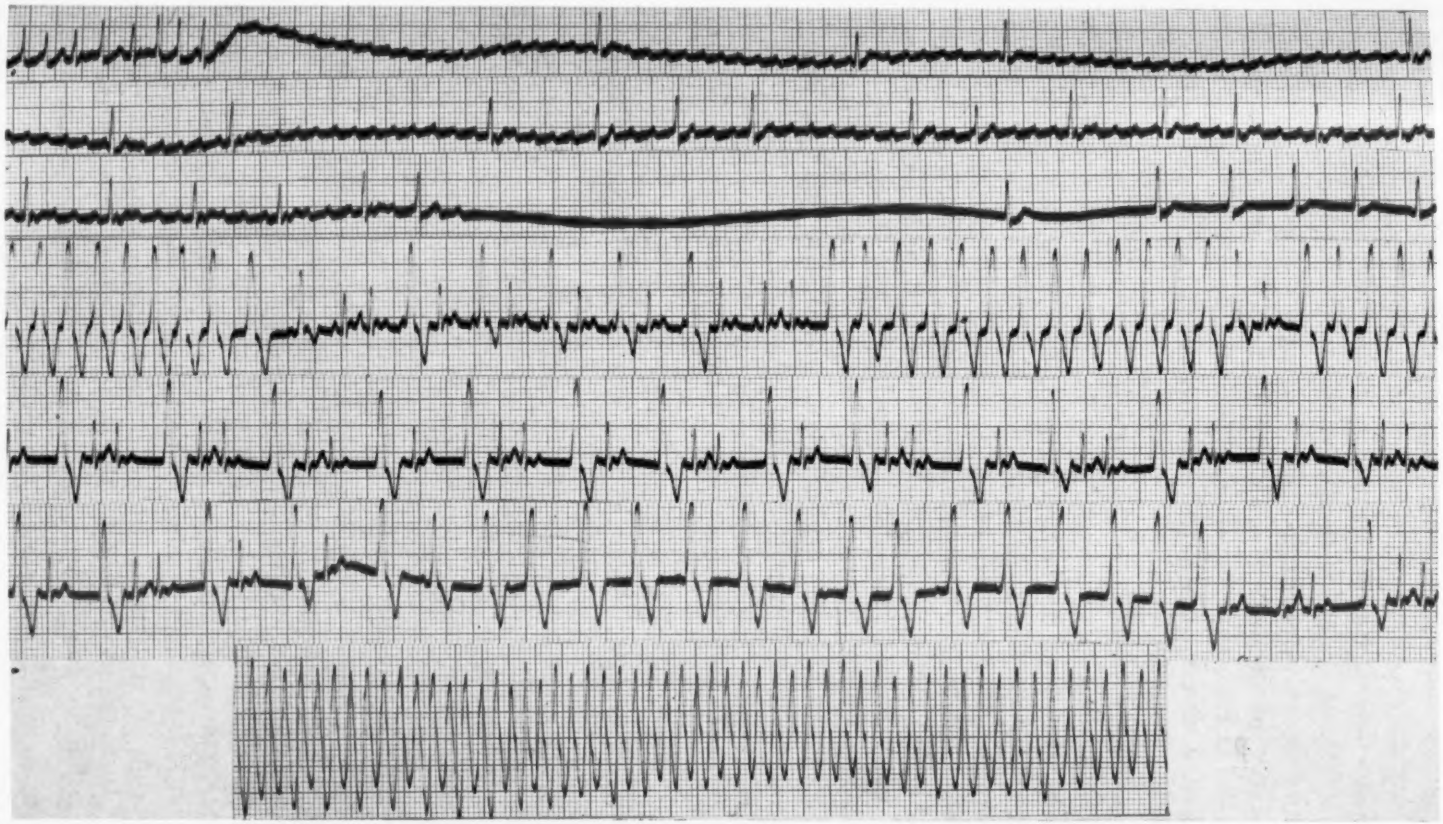

Fig. 6.—Experiment of May 12, 1959. Focal application of aconitine to the sinus node area of the right atrium had caused atrial flutter to appear. Then diphenylhydantoin was injected and the vagus nerve was stimulated, so that the effect of this drug on the atrial electrocardiogram could be studied. The tracing shows that the flutter stops abruptly, without slowing of rate or change in form of the flutter waves (*B* and *C*). An A-V rhythm appeared and changed in a few seconds into sinus rhythm. *A* to *C* are continuous. Atrial flutter reappeared after 2 minutes, and a second injection of diphenylhydantoin again caused an immediate change to sinus rhythm. Aconitine was applied to the ventricles. After 3 minutes and 13 seconds a ventricular tachycardia appeared (*D*). It alternated with periods of ventricular bigeminy, and atrial extrasystoles also reappeared (*E*). During vagal stimulation the bigeminal rhythm was transformed into an irregular ventricular tachycardia (*F*). Later, the heated thermode was applied to the focus of the ventricle to which aconitine had been applied, and a ventricular tachycardia appeared with a rate of 500 beats per minute and alternation of the ventricular complexes. Ventricular fibrillation did not appear in spite of the fast rate (*G*).

The mechanism of the arrhythmia in Fig. 4 is not clear. The P waves remain unchanged throughout. It is possible that we are dealing with the same phenomenon as in Fig. 3, but the absence of postextrasystolic intervals, and the longer atrial intervals, which are about twice the length of the shorter intervals, make it probable that we are dealing with an exit block; a rapid pacemaker is forming impulses regularly but some are not answered by the atria.

The injections of diphenylhydantoin were repeated up to five times in the same experiments, and the injection always had the same result, although, as previously stated, the time required to abolish the arrhythmia was always unpredictable. The dosage necessary to get results was the same regardless of the previous injections.

The effect of diphenylhydantoin on the aconitine-induced ventricular arrhythmias was the same as that on the atrial ones. The appearance of ventricular tachycardia was delayed if, prior to the application of aconitine, the animal had been treated with diphenylhydantoin. In some instances no arrhythmia appeared until the focus of application had been heated by approaching a test tube filled with warm water to the area of application of aconitine without actually being in contact with the heart muscle. After Dilantin, ventricular fibrillation did not appear even when the ventricular rates rose to 500 beats per minute (Fig. 6). Extrasystoles with fixed coupling appeared.

No dilatation, or weakening of the contractility of the heart, was seen after the administration of diphenylhydantoin. The blood pressure was not measured during these experiments since many such studies are available on this subject.

DISCUSSION

In all experiments the existing flutter or fibrillation induced by aconitine or delphinine was rapidly abolished by the intravenous injection of diphenylhydantoin. Sinus rhythm was restored, and when this was inhibited, an A-V rhythm with a rapid rate always replaced it. The effect of diphenylhydantoin on flutter or fibrillation was only temporary, and the abolished arrhythmia returned in all cases within a few minutes. Repeated injections of diphenylhydantoin had the same effect as that of the initial injection, and there was no evidence to indicate a cumulative effect, as the subsequent doses had to remain constant.

The arrhythmia disappeared suddenly or was first changed to extrasystoles, to be followed in a few seconds by a sinus rhythm. A few minutes after the injection, extrasystoles reappeared and gradually increased in number until flutter or fibrillation was re-established.

The marked effect of vagal stimulation on the A-V conduction, and the absence of an effect on the atrial arrhythmia in some experiments is of interest. Atrial extrasystoles due to intravenous application of aconitine are inhibited by vagal stimulation.[10] In the flutter caused by the focal application of aconitine or delphinine there is either no change or an increase in rate during vagal stimulation.[14]

The dose of 5 mg. per kilogram which has been used in the present experiments is relatively small. Gruhzit and Gruber and associates[3,4] found that the

lethal intravenous dose on dogs was 90 mg. per kilogram. When fractional doses were given over a longer period, we found cardiac standstill after 66 to 69 mg. per kilogram.[12] Prolongation of the P-R interval and widening of the QRS complexes are signs of intoxication. It is interesting that ventricular extrasystoles appeared at the height of the toxic effect; this phenomenon is also seen with quinidine and procaine amide.

The first use of Dilantin for cardiac arrhythmias was made by Harris and Kokernot,[5] who studied the effect of the drug on ventricular arrhythmias caused by ligation of the coronary arteries in dogs. They found that with the intravenous dose of 25 mg. per kilogram, ectopic beats were temporarily abolished, and that with doses of 125 to 200, all ectopic beats were suppressed. There was a direct ratio between the number of ectopic beats prior to the injection and the dose of diphenylhydantoin necessary to suppress them. Mosey and Tyler[8] investigated the effect of diphenylhydantoin on ouabain-induced arrhythmias in unanesthetized dogs. The injection of 10 to 30 mg. per kilogram suppressed the arrhythmia in all 12 animals, but it returned between 20 minutes and 2½ hours later. Covino and associates[1] used phenylhydantoin effectively as an antifibrillatory agent in hypothermic dogs; in these experiments, 8 to 50 mg. per kilogram were given, and a marked depression of the sinus node was noted. White and associates[18] noted that the effect of phenylhydantoin on arrhythmias induced by cyclopropane-epinephrine in dogs varied with the dose. Ten milligrams per kilogram of body weight enhanced the arrhythmia, whereas 20 mg. per kilogram depressed it.

The findings in all of these studies are in agreement with our results, that is, diphenylhydantoin suppresses cardiac arrhythmias caused by aconitine or delphinine.

There are only a few observations on the effect of the drug on the human heart. Finkelman and Arieff[2] gave the drug orally and recorded serial electrocardiograms; they noted changes in 25 out of 27 cases. In 13 patients the P-R interval was prolonged by 0.01 to 0.04 second and returned to its former value when the drug was discontinued. A decrease in the T wave was noted in 21 instances. Some patients reported precordial distress.

Tichner[17] described atrial fibrillation and bifocal ventricular extrasystoles in a patient who took diphenylhydantoin for suicidal purpose. However, before the arrhythmia appeared, he had also been given amphetamine.

Another clinical report deserves attention. A 42-year-old hypertensive man developed a ventricular tachycardia in the course of an inferior myocardial wall infarction. This arrhythmia was refractory to procaine amide but responded to 250 mg. of diphenylhydantoin intravenously. The tachycardia recurred after 30 minutes and responded to the same treatment. This treatment had to be repeated twice more in the course of the next few hours, each time with success.

These experiences indicate the need for more clinical studies with this drug, particularly in patients who are suffering from arrhythmias due to digitalis toxicity or secondary to myocardial infarction. Under certain conditions the transitory nature of the effect of diphenylhydantoin will be a handicap. The doses employed by us were in excess of those used in patients with status epilepticus.[9] In view of the difficulty in abolishing even temporarily the fibrillation caused by

focal application of aconitine with drugs given intravenously, it is probable that clinical arrhythmias will respond to much smaller doses.

The mode of action of diphenylhydantoin on flutter and fibrillation is not known; however, it is of interest that in rats treated with this substance, the brain, skeletal muscles, and heart muscle showed a decreased amount of intracellular sodium. An increase in the movement of radiosodium in and out of the cells was also seen in the same series of experiments.[19]

SUMMARY

In dogs anesthetized with Nembutal and morphine the heart was exposed, and aconitine or delphinine crystals were applied to the surface of the right atrium in order to create flutter or fibrillation. The effect of the intravenous administration of diphenylhydantoin sodium (Dilantin) on these arrhythmias was studied. In 14 experiments with aconitine and 8 with delphinine, sinus rhythm was obtained quickly, and in 20 of the 22 experiments it was obtained abruptly by the intravenous injection of 5 mg. per kilogram of diphenylhydantoin. This effect was transient, since the atrial arrhythmias reappeared within a few minutes. Repetition of the injection (up to five injections in a single experiment) had the same effect as that of the first injection.

Ventricular tachycardias provoked by the topical application of aconitine crystals on the right ventricle responded in the same way as did the atrial flutter and fibrillation.

Special characteristics of atrial and ventricular arrhythmias caused by diphenylhydantoin are described. The experimental and clinical literature dealing with the action of diphenylhydantoin on cardiac arrhythmias is discussed.

We wish to thank Mr. W. L. Schrier, of Parke, Davis & Company, for the supply of some quantities of diphenylhydantoin used in this study.

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Effect of Heart Size on the Oxygen Uptake of the Myocardium

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Recently, considerable emphasis has been placed on the importance of the law of Laplace in determining the oxygen uptake of the beating mammalian heart.[1] In accordance with this law, a large or dilated ventricle with radii of curvature greater than those of a small or nondilated heart must develop more intramural tension (force of contraction) in order to generate a given intraventricular pressure. In a hollow, perfectly spherical body with a distensible membrane of negligible thickness the relationship, according to Laplace, is:

$$T = \tfrac{1}{2} R P$$

where T is the tension in the membrane, R is the radius of the sphere, and P is the pressure in the cavity. It has been suggested that the ventricular myocardial tension during systole or ejection may be one of the chief determinants of the oxygen requirement of the pumping heart.[2,3]

Although these studies have pointed out the influence of increased heart "size" on myocardial energy expenditure, yet distinction has not been made between anatomically large hearts and those that are simply dilated. The importance of the thickness of the ventricular walls and the total mass of tissue in developing the tension and their influence on the metabolic rate per unit weight of tissue have not been adequately considered. It has been well documented that an increase in cardiac "size" brought about by an acute dilatation of the chambers of the heart increases the energy cost of contraction in accordance with the law of Starling, other factors remaining the same. Here, oxygen uptake per unit weight of tissue is increased. However, no study has been made comparing the energy cost of cardiac activity per gram of tissue in a small heart having relatively thin ventricular walls and small radii of curvature with that of an anatomically large heart with thicker walls and larger radii of curvature in a given species.

This report deals with a study of the oxygen uptake of the heart per unit weight of tissue in a series of small and large hearts in the heart-lung preparation as modified in our laboratory.[4,5]

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METHODS

Heart-lung preparations (HLP) were used on two groups of mongrel dogs: (1) small dogs of both sexes which weighed 8 to 11 kilograms, and (2) large dogs which weighed 21.5 to 25 kilograms. Since it was impossible to rule out age differences, animals which belonged to extreme age groups were avoided as much as possible. As a rule, the experiments on small and large dogs were conducted alternately.

Fig. 1 illustrates the modified HLP used. The superior vena cava was ligated instead of being cannulated, and the systemic blood from the venous reservoir was led to the right lung by cannulating the right pulmonary artery. The right heart pumped only the coronary venous blood into the left lung. The coronary flow was measured with a rotameter[6] in the left pulmonary artery. Under conditions of steady state, cardiac oxygen consumption was determined by the direct Fick method.

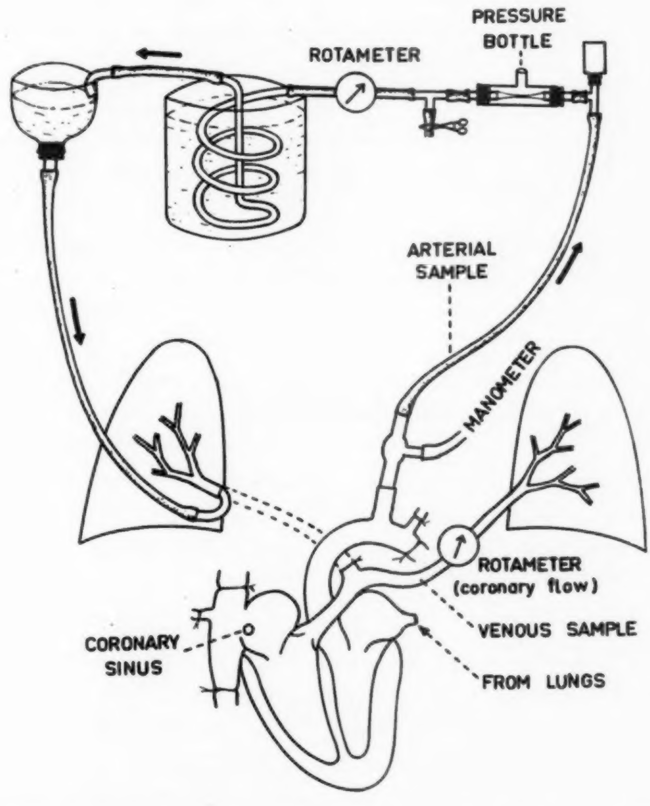

Fig. 1.—Modified heart-lung preparation for the determination of the oxygen uptake of the heart by the direct Fick method.

In the present study, good arterial saturation was obtained by preventing the complete collapse of the lungs with the use of 3 to 5 cm. of water resistance on the expiratory tube of the Starling pump. The lungs were inflated either with room air or with 100 per cent oxygen. The output of the left ventricle was set at about 1 liter per minute, and the mean aortic pressure at 100 mm. Hg, with particular attention being paid to keep the latter as constant as possible. The temperature of the heart was recorded by means of a needle thermocouple inserted into the left ventricular myocardium near the apex. (In a few experiments this led to frequent ectopic beats, and the thermocouple had to be removed.) The heart rate was kept constant at about 150 beats per minute with the use of a Grass electronic stimulator. The electrodes were applied to the tip of the right atrial appendage, and monophasic pulses of 3-volt intensity and 2-millisecond duration

were used. (In some experiments the sinoatrial rhythm was around 150 per minute and the stimulator was not used.)

When a steady state was reached (45 to 75 minutes after the establishment of the artificial circuit), the respiratory pump was temporarily stopped, since it caused fluctuations in coronary flow as measured in the left pulmonary artery. During this short period the flow was noted, after which arterial and venous samples were taken simultaneously and analyzed for oxygen by the Van Slyke manometric technique.

At about 5-minute intervals, two more determinations of the oxygen uptake of the heart were made. Experiments with poor checks were discarded.

At the conclusion of most experiments the left ventricle was cut longitudinally midway between the interventricular groove and the left border of the heart. The thickness of its wall was measured at a distance of 1.5 cm. from the tip of the apex.

Cardiac work was calculated as follows:

L.V. Work (Kg.-M./min.) = L.V. output (L./min.) × aortic pressure (meters) × 13.6

R.V. Work (Kg.-M./min.) = R.V. output (L./min.) × pulmonary arterial pressure (meters) × 13.6

RESULTS

The data of 10 experiments on small hearts are shown in Table I. The mean oxygen uptake of the heart per 100 grams of tissue per minute was 6.76 ml., S.E. ± 0.29. The average heart weight was 69.5 grams, with a left ventricular thickness of about 9 mm. On 10 large dogs with a mean heart weight of 158.5 grams, the average oxygen consumption of the heart was 6.56 ml. per 100 grams per minute, S.E. ± 0.27 (Table II). The mean left ventricular thickness was 11.1 mm.

In both groups of experiments the mean left ventricular myocardial temperature was 36.9°C., with a mean rate of 150 beats per minute, and the heart performed the same pressure-volume work. The arterial blood was well saturated with oxygen, as indicated by its high content (21 volumes per cent). The coronary blood flow per unit weight of tissue and the oxygen content of coronary venous blood were about the same in the two series.

DISCUSSION

In these experiments it was assumed that in the anatomically larger hearts the ventricular end-systolic blood volume was greater than in the smaller hearts, although the stroke volume was the same. This would imply that the ventricular walls operated with larger radii of curvature (Fig. 2).

If the law of Laplace for a sphere applies to the beating heart, the tension in the wall of the larger heart must be greater in order to generate a given intraventricular pressure. Peterson[7] has pointed out that the law was stated for a static membrane which is thin in comparison to its radius of curvature. In the case of the ventricles, particularly the left one, the wall is thick relative to the radius, and the "membrane" is dynamic, changing its radius and thickness during the period of ventricular ejection.[3] The inner and outer layers of muscle have appreciable differences in radii, and whether or not the outermost layers of the ventricular myocardium are subjected to the same radial pressure as the innermost ones remains uncertain. The fact that the ventricles are not perfectly spherical is not a serious difficulty because the law applies to nonspherical and even to cylindrical bodies. The general equation of Laplace is:

TABLE I. MODIFIED HLP ON SMALL DOGS

EXPERIMENT NUMBER	DOG WEIGHT (KG.)	HEART WEIGHT (GM.)	LEFT VENTRICULAR THICKNESS (MM.)	RIGHT VENTRICULAR OUTPUT (ML./MIN.)	LEFT VENTRICULAR OUTPUT (ML./MIN.)	CARDIAC WORK (KG.-M./MIN.)	CORONARY BLOOD FLOW (ML./100 GM./MIN.)	ARTERIAL O_2 CONTENT (VOL.%)	CORONARY A-V O_2 DIFFERENCE (VOL. %)	MYOCARDIAL O_2 UPTAKE (ML./100 GM. /MIN.)
4	8.0	55	—	30	998	1.37	54	21.61	13.75	7.42
6	9.1	62	—	36	1,002	1.37	58	21.68	11.69	6.69
8	8.8	59	—	33	989	1.35	56	23.88	14.09	7.89
10	9.7	67.5	8	35	1,002	1.37	51.3	20.74	12.20	6.25
12	10.0	75	8	31	991	1.35	40.9	24.80	15.02	6.15
15	11.0	89	9	52	1,020	1.39	58.7	17.18	9.59	5.63
19	10.2	82.5	10	31	994	1.37	37.6	19.60	15.05	5.66
20	8.7	64	9	48	1,008	1.38	74.5	17.58	8.20	6.08
22	9.3	76.5	9	50	971	1.33	65.0	21.30	11.98	7.78
24	8.5	64	10	56	992	1.36	88.1	21.72	9.13	8.02
Mean	9.3	69.5	9	40	997	1.36	58.4	21.01	12.07	6.76 S.E. ± 0.29

Mean aortic pressure = 100 mm. Hg. Mean pulmonary arterial pressure assumed to be 15 mm. Hg. Mean left ventricular myocardial temperature = 36.9° C. (36.2–37.8). Mean heart rate = 149/min. (144-153). In each experiment (except No. 6) the values represent the average of three check determinations at intervals of 5 minutes.

TABLE II. MODIFIED HLP ON LARGE DOGS

EXPERIMENT NUMBER	DOG WEIGHT (KG.)	HEART WEIGHT (GM.)	LEFT VENTRICULAR THICKNESS (MM.)	RIGHT VENTRICULAR OUTPUT (ML./MIN.)	LEFT VENTRICULAR OUTPUT (ML./MIN.)	CARDIAC WORK (KG.-M./MIN.)	CORONARY BLOOD FLOW (ML./100 GM./MIN.)	ARTERIAL O_2 CONTENT (VOL.%)	CORONARY A-V O_2 DIFFERENCE (VOL. %)	MYOCARDIAL O_2 UPTAKE (ML./100 GM./MIN.)
3	22.5	150	—	73	1,033	1.42	48.5	20.85	11.36	5.50
5	22.0	137	—	65	1,025	1.41	47.7	23.47	14.84	7.03
7	25.0	195	—	101	1,037	1.43	52.0	24.33	13.63	7.07
9	21.6	140	10	60	1,013	1.39	43.0	20.84	13.07	5.60
11	21.5	167.5	12	63	999	1.37	37.6	21.14	13.96	5.25
13	23.5	167.5	11	139	1,075	1.49	82.8	17.41	8.27	6.74
16	25.0	160	11	98	1,034	1.43	61.0	18.13	11.72	7.10
17	24.4	160	11	64	1,012	1.39	40.2	24.56	15.75	6.33
18	23.3	170	11	85	1,021	1.40	50.0	23.59	14.05	7.00
23	24.7	138	12	143	995	1.38	103.4	22.59	7.73	7.98
Mean	23.3	158.5	11.1	89	1,024	1.41	56.6	21.69	12.44	6.56 S.E. ± 0.27

Mean aortic pressure = 100 mm. Hg. Mean pulmonary arterial pressure assumed to be 15 mm. Hg. Mean left ventricular myocardial temperature = 36.9° C. (36.6-37.3). Mean heart rate = 150/min. (145-155). In each experiment (except No. 7) the values represent the average of three check determinations at intervals of 5 minutes.

$$T = \frac{P}{\frac{1}{R_1} + \frac{1}{R_2}}$$

where R_1 and R_2 are the maximum and minimum radii of curvature at any one point. For details, the reader must consult Burton's paper.[1] These considerations suggest that the law of Laplace cannot be applied to the heart in a simple manner. Nevertheless, the influence of the various factors involved can be utilized in a general way, just as Poiseuille's law can be used for understanding the basic principles of hemodynamics.

Our results showed that the oxygen consumption of the myocardium per unit weight of tissue was the same in the large and small hearts. Consequently, the larger hearts had a greater total oxygen uptake simply as a result of the greater number of contractile units. The greater tension developed by the wall of the larger heart, as required by the Laplace formula, was produced by the greater thickness and circumferential length of the ventricular walls (Fig. 2).

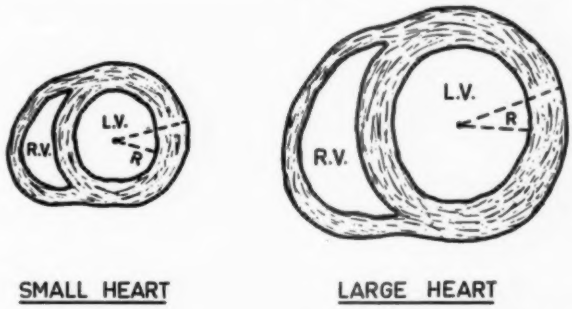

Fig. 2.—Cross section of ventricles in hearts of different anatomic size (end-diastolic). Note the differences in the radii of curvature, thickness of walls, and circumferential length of muscle. When stroke volume is the same in both, the end-systolic blood volume must be greater in the larger heart.

It should be noted that in the application of the Laplace equation to the heart, T represents the tension developed by the entire thickness of the myocardium at any region of the heart. Therefore, when the formula is used for hearts of different anatomic size, due consideration must be given to the thickness of the myocardium in generating the tension. To avoid confusion, it would be best to express tension per unit thickness and length of muscle (cross-sectional area), as discussed by Burton.[1]

The situation is quite different when a given heart is acutely dilated either by increased diastolic filling or by increased end-systolic blood volume. The tension in the wall during systole would increase in accordance with the law of Laplace. Since the number of contractile units remains the same, the force or tension generated per unit weight of tissue would increase. This would account for the increase in the oxygen uptake per unit weight, provided that the tension hypothesis is true.

The results of our experiments may have a bearing on studies of the metabolic rate of hypertrophied heart muscle. In patients with essential hypertension it has been noted that the oxygen uptake of the hypertrophied left ventricle was

the same as that of normal per unit weight of heart tissue.[8] This was confirmed by West and co-workers[9] in nonanemic renal hypertensive dogs in which the metabolic rate of hypertrophied left ventricle per gram of tissue was found to be the same as that in normotensive controls. However, in both of these studies the hypertrophied ventricle was performing more pressure-work than the control. In view of the probable role of the law of Laplace and of myocardial tension in cardiac metabolic rate, measurement of the ventricular end-systolic blood volume assumes great functional importance since it affects the radius of curvature and the tension in the wall. Unfortunately, the method of determining this volume is elaborate,[10] and it was not feasible in our experiments to carry out this measurement simultaneously with the determination of the oxygen uptake of the heart.

SUMMARY

Recent studies suggested that myocardial tension during systole was an important determinant of cardiac oxygen consumption. According to the law of Laplace, a large or dilated ventricle must develop more tension in its walls than a smaller one in order to generate a given luminal pressure and is, therefore, expected to have a greater oxygen uptake. The effect of the anatomic size of the heart on the oxygen uptake per unit weight of myocardium was investigated. Experiments on the heart-lung preparation of the dog showed that the oxygen uptake in anatomically large and small hearts was the same per unit weight of tissue when aortic pressure, cardiac output, heart rate, and myocardial temperature were constant. The conclusion was that the larger heart developed more tension in its walls and used more oxygen in direct proportion to its greater number of contractile units or weight. The application of the Laplace formula to the heart must take into account the thickness and circumference of the ventricles.

The technical assistance of Mr. A. Tchelebian is gratefully acknowledged.

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Case Reports

Functional Subaortic Stenosis Due to Cardiomyopathy of Unknown Origin

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The rapid developments in the field of open-heart surgery for acquired valvular lesions has placed increasing responsibility on the cardiologist for accuracy in the diagnosis and selection of cases for definitive correction. Recent experience has demonstrated a type of normotensive, low-output cardiopathy involving the left ventricle, which mimics closely the clinical picture of aortic valvular stenosis. These cases, however, have been found to present no evidence of anatomic obstruction to left ventricular ejection. Indeed, there is instead a physiologic "systolic stenosis" of the left ventricular outflow tract due to muscular hypertrophy, which reproduces closely the same state of disturbed circulatory dynamics presented by organic obstruction at this point.

It is our purpose to report 2 cases demonstrating this clinical entity. Both of these patients died as a result of ill-advised cardiotomy subsequent to mistaken diagnoses. Although in recent years there have been a few reports[1-4] in the literature on this subject, only one[4] has referred to the distinctive character of the brachial arterial pulse contour as a clue to accurate diagnosis. This presentation corroborates this feature and calls further attention to the other distinguishing variations in the clinical picture. It is anticipated that more widespread awareness of this problem will promote more dependable recognition before the patient is subjected to needless and disastrous surgery.

CASE REPORTS

Case 1. (L. V. H.).—This 39-year-old white woman was first seen in May, 1955, at which time she gave a history of having had frequent severe attacks of tonsillitis as a child, but no other history to suggest rheumatic fever. At the age of 12, she was first told that she had a "rheumatic heart." It is not known whether her heart was enlarged at that time; it is known that she had no physical limitations. In September, 1950, she was found to have slight cardiac enlargement and a loud basal systolic murmur. The electrocardiogram showed evidence suggestive of left ventricular

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hypertrophy. Blood pressure was 110/64 mm. Hg. There was additional past history that she had had a duodenal ulcer with hemorrhage in 1945. The family history was noncontributory.

The only complaints on the initial visit to our offices in 1955, were palpitation and breathlessness which occurred mainly under emotional stress. Examination at that time revealed normal vital signs, including a blood pressure of 120/70 mm. Hg. The only abnormal findings noted were related to the heart. There was a normal sinus rhythm, with a rough, blowing, systolic, Grade 4 murmur, loudest at the apex but radiating in all directions. The heart was enlarged to the left.

Chest roentgenograms revealed left ventricular enlargement, with minimal left atrial dilatation and a prominent pulmonary artery. The electrocardiogram revealed left ventricular hypertrophy and a normal sinus rhythm. The clinical impression was rheumatic mitral insufficiency.

The patient did well until 1957, at which time she suffered a reactivation of the duodenal ulcer. This responded to the usual measures. However, in September, 1957, it was noted that the heart size was increasing. Furthermore, on the basis of fluoroscopy, the left atrium seemed to be more dilated than it was previously.

In June, 1958, the heart size was found to be still larger, and by January, 1959, she began to complain of dizziness and vague upper abdominal distress. The liver was found to be slightly enlarged and sensitive to palpation. Radiographic comparison with previous films showed that again the heart size had increased. The patient was then digitalized.

In early March, 1959, auricular fibrillation was noted for the first time, and on March 28, 1959, the patient suddenly developed a left hemiplegia. In spite of the history of an ulcer, anticoagulant therapy was instituted. Recovery from the hemiplegia was progressive, and in June, 1959, she was referred to Dr. Earle Kay and Dr. Henry Zimmerman, in Cleveland, Ohio, for possible surgical correction of the mitral insufficiency.

Right heart catheterization was performed by Dr. Zimmerman, with the following result: (1) no intracardiac shunts demonstrated, (2) slight elevation of the pulmonary arterial pressure of 45/27 mm. Hg, and (3) moderate elevation of the pulmonary wedge mean pressure of 27 mm. Hg.

It was their preoperative impression also that this patient had mitral regurgitation, and surgery was performed. However, the mitral valve was found to be entirely normal, with no evidence of either regurgitation or stenosis. A deposit of calcium was found in the ring anteriorly, which seemed to arise from the aortic valve, and the left ventricular muscle was found to be markedly hypertrophied, to the extent that there was very little ventricular chamber present. Measurements of pressure were made between the left ventricle and the aorta: the pressure was 180/8 mm. Hg in the former and 100/80 mm. Hg in the latter. Left auricular pressures at surgery were 39/15 mm. Hg. It was the impression of the operating surgeon, Dr. Kay, that aortic stenosis existed.

At the time of this operation no definitive correction was made, and it was the intention of the surgeon to carry out surgical correction of the aortic valvular lesion at a subsequent date. However, on the ninth postoperative day the patient had a massive cerebral embolism and subsequently died. Autopsy revealed marked left ventricular hypertrophy, as described at surgery. As will be noted in Fig. 1, the muscular hypertrophy also involved the right ventricle, although the enlargement was not entirely symmetrical. There were, in addition, minimal changes along with a calcified area in the mitral leaflets, which led to a pathologic diagnosis of rheumatic valvular disease. It was the opinion of the pathologists, however, that this valvular disease was not sufficiently abnormal to derange the cardiac hemodynamics. The final diagnosis was cardiac hypertrophy of undetermined cause.

CASE 2. (J. W.).—This 57-year-old white woman, a widow, was seen on Oct. 31, 1959, because of increasing intensity and frequency of angina pectoris, shortness of breath, and faintness on slight exertion. There was profound weakness and fatigability dating back to May, 1959, when all of these complaints had started rather abruptly during convalescence from an acute respiratory infection. Angina pectoris, secondary to exercise or emotional stress, was present at the start, but attacks became spontaneous in August, 1959, and continued with increasing frequency. A short period of hospitalization was required after a particularly severe and prolonged episode of chest pain. There was no past history of hypertension or rheumatic fever, but in 1950, a hysterectomy was complicated by a transient left hemiplegia, attributed to a cerebral embolus, although a regular rhythm was present. A year later the patient was hospitalized again, with a

recurrence of the hemiplegia, which was this time associated with left hemifacial pain. After thorough neurological study a diagnosis of cerebral thrombosis was made. She regained about 95 per cent of function, and in spite of a sense of fatigue she was generally active and well. In January, 1958, she had a mild case of viral hepatitis and made an uneventful recovery. The blood pressure was recorded as 120/70 mm. Hg during this admission.

The patient stated that a definite change in her over-all well-being actually occurred in May, 1959, with this date marking the onset of marked physical limitations. At no time in the past had the presence of a murmur been mentioned to the patient by her medical advisors, and none was recorded on the previous hospital records. The family history was entirely noncontributory.

Fig. 1.—Cross-sectional views of the autopsy specimen of the heart in Case 1. Note the hypertrophy of both cardiac chambers.

Physical examination revealed a chronically ill-appearing woman who was quite pale. Cool perspiration was present on the face. The blood pressure was 100/70 mm. Hg, and the heart rate was 100 per minute. Palpation of the left precordium demonstrated enlargement of the left ventricle. The second sound over the aortic area was markedly diminished to absent. A Grade 3 pansystolic murmur was heard over the entire precordium; it was loudest at the apex, with some transmission to the left axilla. Equivocal transmission to the carotid vessels was noted. The peripheral pulse volume was extremely small. A few scattered crepitant inspiratory râles were present at the bases of both lungs. Minimal residual weakness in the left arm and leg was detected.

Routine laboratory studies were essentially normal. Four electrocardiograms were available for review, dating back to 1955. Each was abnormal, showing increasing evidence of left ventricular hypertrophy and strain. The final tracing, recorded on Nov. 2, 1959, is illustrated in Fig. 2 and demonstrates typical systolic overloading hypertrophy of the left ventricle. A chest roentgenogram

revealed left ventricular enlargement with scattered areas of discoid atelectasis in both mid-lung fields (Fig. 3). Comparison of this latest film with others dating back to 1950, showed a moderate increase in heart size. Fluoroscopy and lateral films did not show evidence of valvular calcifications, and no poststenotic dilatation of the ascending aorta was present.

A clinical differential diagnosis included: (1) severe aortic stenosis with an atypical murmur, and (2) subendocardial infarction and ruptured papillary muscle with mitral insufficiency.[5,6]

Even with hospital bed rest the patient continued to be symptomatic, and often the skin was observed to be cool and clammy. Blood pressure ranged from 70/40 to 90/70 mm. Hg, with a heart rate of from 100 to 120 which failed to slow appreciably with digitalization.

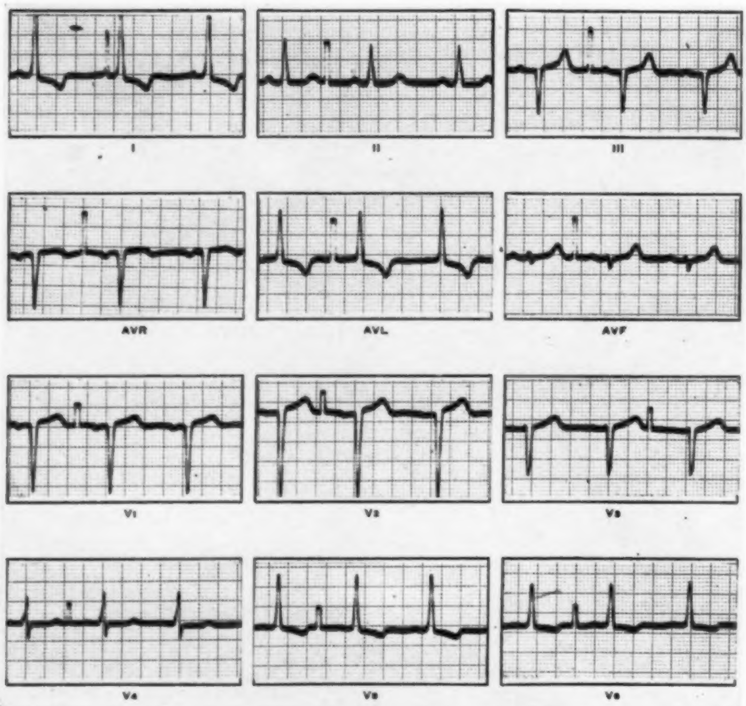

Fig. 2.—Electrocardiogram in Case 2, showing typical left ventricular hypertrophy of the systolic overloading type.

An indirect carotid pulse tracing was obtained because the extremely small pulse volume prevented direct cannulation of the brachial artery percutaneously. The pulse wave (Fig. 4) had an unusual bisferiens-like character, but not of the double-peaked type seen with aortic insufficiency. It also demonstrated a narrow pulse pressure and a markedly delayed systolic ejection tidal wave and dicrotic notch. At this time the features of this curve were erroneously attributed to the technical inaccuracies of an indirect tracing. Right heart catheterization showed no evidence of an intracardiac shunt; the pulmonary wedge mean pressure was 12 mm. Hg and the contour was normal; pulmonary arterial pressure was slightly increased at 35/17 mm. Hg; and cardiac output was low and relatively fixed. Left heart catheterization was not performed.

Progressive deterioration of the patient led to open-heart surgical exploration by Dr. Denton Cooley, on Dec. 10, 1959, since it was the opinion that either of the suspected lesions might be corrected surgically. The exploring finger in the left atrium revealed a small intermittent regurgitant jet across the anterior leaflet of the mitral valve. Under direct vision, a pathologic tear into the mid-portion of this leaflet was observed. The aortic valve was entirely normal, and no anatomic obstruction to the aortic outflow tract of the left ventricle was observed. The musculature

of the left ventricle was extremely thick, and the chamber was reduced in size to such an extent that the surgeon's finger was barely admitted. In spite of all efforts to support the patient after discontinuance of extracorporeal circulation, she died on the surgical table.

Autopsy revealed diffuse cardiac hypertrophy involving both ventricles, but primarily the left one. The heart weighed 470 grams. The essential findings were the same as those noted at surgery. Both mitral leaflets were slightly thickened and there were several small, smooth nodula-

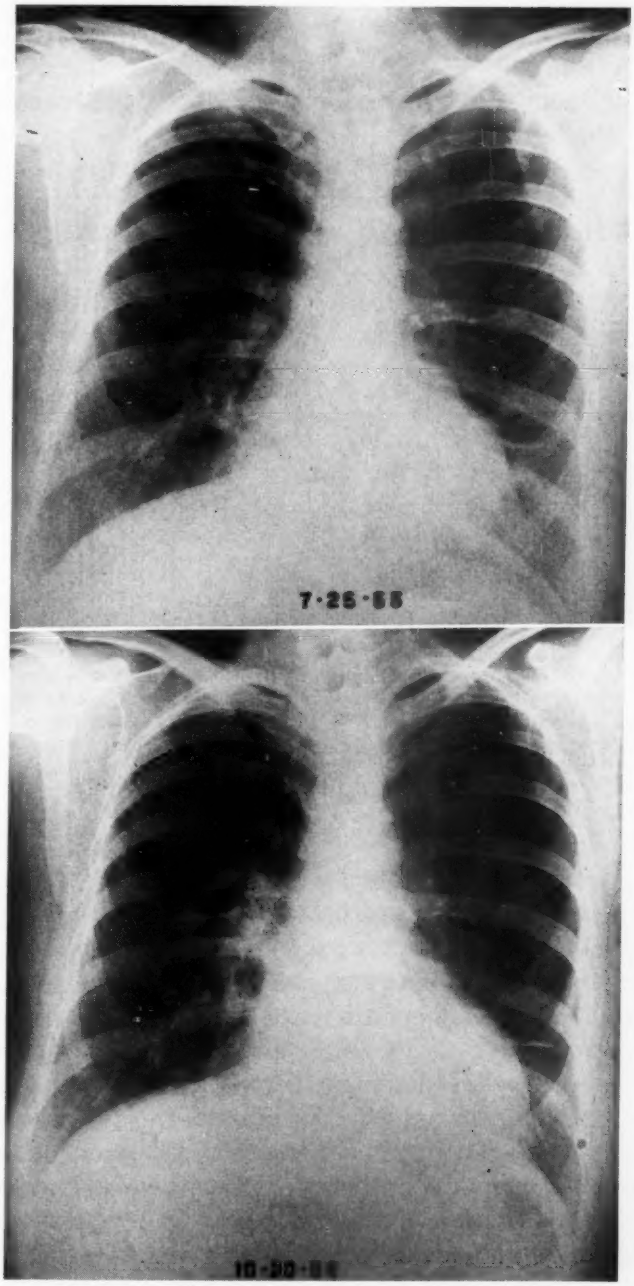

Fig. 3.—Frontal plane chest roentgenograms for comparison of heart size in Case 2.

tions along the edges of the cusps, with slight fibrous thickening of the chordae tendineae. It was the pathologist's opinion that these findings were insufficient to explain the degree of muscular hypertrophy present. The coronary vessels were slightly sclerosed, but widely patent. The final diagnosis was cardiac hypertrophy of undetermined cause.

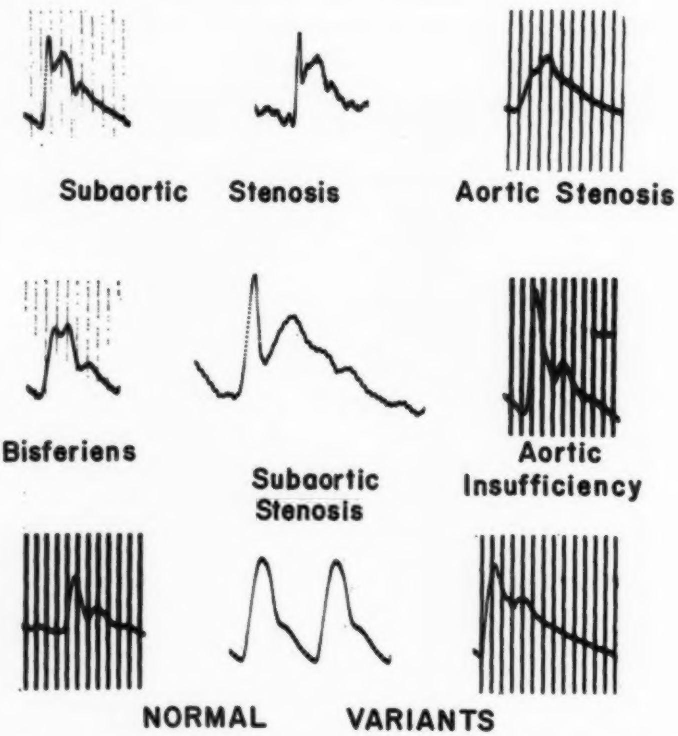

Fig. 4.—Arterial pulse tracings. Tracing (*upper center*) at 25 mm. per second film speed and (*mid-center*) at 75 mm. per second film speed are those of Case 2. Note the distinctive prominent and rapidly ascending percussion wave followed by a delayed tidal wave and dicrotic notch. These are indirect carotid tracings, whereas all other illustrations for comparison purposes are direct brachial arterial pulses (see text for discussion).

DISCUSSION

There is no real difficulty presented in understanding organic types of subvalvular aortic stenosis, but not until recent years has the alternative form of functional or muscular aortic subvalvular stenosis been described. Only 5 patients who have presented the set of circumstances seen in these 2 cases have been reported upon in the medical literature[1,3,4,7] Similarly, in each instance, surgical exploration was carried out with the intention of correcting either aortic or subaortic stenosis. Likewise, the final diagnosis in each case was ventricular hypertrophy of uncertain cause which produced functional subvalvular aortic stenosis. Brachfeld and Gorlin,[4] in their recent comprehensive review of the subject, list idiopathic myocardial hypertrophy as one of the miscellaneous causes for muscular subaortic stenosis of either acquired or developmental origin. However, only 1 of their 4 cases which ultimately came to either surgical or postmortem examination presented pure ventricular hypertrophy with four normal cardiac valves. The other patients demonstrated an associated subaortic fibrous

band in addition to hypertrophy of the septal wall. Two additional unproved cases were reported which present strong supportive evidence for this diagnosis. These authors, furthermore, suggest that the fibrous band so often seen in cases of so-called subaortic stenosis may, in effect, be secondary to the primary myocardial hypertrophy which, in turn, leads to traumatic endocardial sclerosis in a region of functional outflow tract obstruction. A review of all these cases, nonetheless, has demonstrated the poor tolerance for even moderate surgical trauma, and all efforts at resection of the outflow tract have proved futile, thus emphasizing the inoperability of this state. For this reason alone, it must be considered and diagnosed if possible without surgical exploration.

Brock[2] was the first to recognize that a central mechanism in the outflow tract could produce functional subvalvular stenosis. Because this was observed in the right ventricle to be responsible for failure to relieve pulmonary valvular stenosis adequately even after open operation, it seemed reasonable to assume that a similar situation could occur in the left ventricular outflow tract. Thus, it was subsequently found that some patients with aortic valvular stenosis who failed to obtain benefit from technically satisfactory valvulotomy demonstrated evidence of definite infundibular obstruction in pull-back pressures from the aorta to the left ventricle. Two cases were reported in which apparent aortic valvular stenosis developed quickly during the late phases of a long-standing systemic hypertension. A presumptive diagnosis of functional subvalvular stenosis was established by withdrawal pressure records made at operation, and the absence of valvular stenosis was confirmed at autopsy. It was suggested that this phenomenon most satisfactorily accounts for the clinical fall in blood pressure, often observed in the late stages of hypertensive disease. The left ventricular pressure, of course, remains high or is even aggravated further under these circumstances.

In 1958, Bercu[1] reported upon a patient with left ventricular hypertrophy of unknown cause simulating aortic stenosis in whom a large systolic pressure gradient across the aortic valve was demonstrated. In spite of an atypical murmur it was decided that surgery to correct aortic stenosis was indicated. No evidence of aortic block was discovered, however, and postoperatively the patient died. It was noted at exploration that both ventricular cavities were reduced to mere uniform slits throughout the entire length and including the apices. At autopsy the mass of hypertrophied muscle weighed 770 grams. The heart did not appear to fulfill the criteria for the entity referred to as idiopathic ventricular hypertrophy since the heart was not dilated, there was no evidence of congestive failure, nor was there pulmonary embolization. All of these features are characteristic of the clinical picture described by Spodick[8] in his review of the subject. Bercu failed to indicate any possible clinical means of distinguishing cases of subaortic stenosis due to muscular hypertrophy from those of aortic valvular stenosis.

Subsequently, Morrow[3] reported upon 2 patients demonstrating pressure gradients across the aortic valve who failed to present an anatomic site of outflow obstruction at the time of open-heart operation. Both of these patients were younger than either of our patients or the one reported by Bercu, and, fortunately, they survived their operation. In one of these who was ultimately studied by

selective left ventricular angiocardiography, an area of systolic narrowing in the left ventricular outflow tract was clearly outlined, associated with mitral insufficiency. It was obvious from this case that the obstruction to ventricular outflow was of such a nature that it was only operative in the contracting heart and was not apparent in the diastolic paralysis induced by potassium citrate at the time of extracorporeal surgery. The only explanation would appear to be muscular hypertrophy severe enough to produce systolic stenosis of the left ventricular outflow tract. It was this author's opinion that the most definitive diagnostic technique in distinguishing from other forms of aortic stenosis is selective left ventricular angiocardiography, preceded by complete left heart and aortic catheterization for demonstration of the pressure gradient.

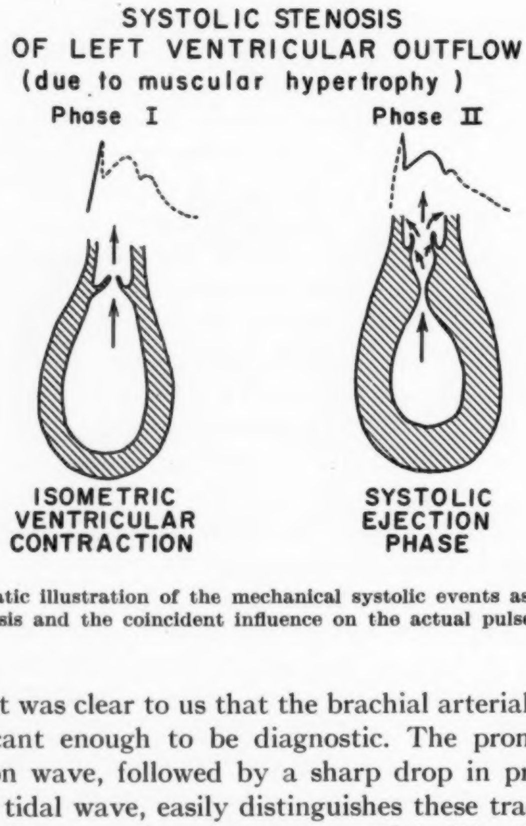

Fig. 5.—Diagrammatic illustration of the mechanical systolic events associated with functional subvalvular aortic stenosis and the coincident influence on the actual pulse tracing (modified after Brachfeld[4]).

In retrospect, it was clear to us that the brachial arterial pulse tracing gives information significant enough to be diagnostic. The prominent and rapidly ascending percussion wave, followed by a sharp drop in pressure and a more slowly rising broad tidal wave, easily distinguishes these tracings from those of aortic stenosis or other normal variants, as noted in Fig. 4. Furthermore, the peak of the tidal wave or secondary wave, as well as the dicrotic notch are both markedly delayed beyond the expected normal. One might surmise that early normal systolic ejection is abruptly interrupted by premature constriction of the outflow tract before the left ventricular chamber is empty (see Fig. 5). With continued isotonic contraction this functional resistance is gradually overcome by a greatly increasing intraventricular pressure, and retarded systemic ejection is then completed, with inscription of the secondary wave in the brachial pulse. This secondary peak coincides in time with the delay seen in pure valvular stenosis, and actually the tracing resembles somewhat a bisferiens pulse.

Soon after our experience with this second case, Brachfeld and Gorlin[4] reported this same phenomenon: the characteristic arterial pulse curve was observed in 3 proved cases of congenital subaortic stenosis, 1 proved case of functional subaortic stenosis due to left ventricular hypertrophy, and 1 additional case of suspected subaortic stenosis which has not yet been established by anatomic examination. They further affirmed the observation that some patients with massive left ventricular hypertrophy present a different physiologic obstruction to flow than do those patients with a tight valvular stenosis or a tight subvalvular fibrous band. It was their belief that the septal hypertrophy assumes the greatest role of importance during the later phases of isotonic contraction and sets up eddy currents which delay total ejection and permits a delayed tidal wave to form.

Brock, Morrow, and Brachfeld emphasized the fact that patients presenting atypical clinical features of aortic stenosis should be studied carefully for roentgenologic evidence of aortic valvular calcification, as well as poststenotic dilatation of the ascending aorta. Aortic valvular calcification can be expected in 87 to 97 per cent of the patients with aortic valvular stenosis, whether congenital or rheumatic, and becomes of progressively greater significance with advancing age. Dilatation of the ascending aorta is the most consistent roentgenologic abnormality in patients with congenital aortic stenosis and is found in over 80 per cent of these patients. On the other hand, 90 per cent of the patients with proved subaortic stenosis will fail to demonstrate this finding.

Thus, when both of these important roentgenologic features are found to be absent in a patient suspected of having aortic block clinically, when an atypical murmur is present, and when a direct brachial arterial curve reveals the features described, it becomes essential that both left heart and aortic pressures be measured. If a pressure gradient of some magnitude is obtained with a pull-back curve that suggests an infundibular chamber, then a definite diagnosis of functional aortic subvalvular muscular stenosis will be made with greatest certainty by selective left ventricular angiocardiography. Further corroboration may be obtained by the demonstration of the same percussion wave noted peripherally also in the subaortic chamber.

As to the etiology of the ventricular hypertrophy in the patients reported upon here, much is unknown. The coronary arteries were widely patent and there was no evidence of fibroelastosis. The myocardium appeared normal in color and consistency. The lack of a family history of a similar disorder precludes the possibility that these cases represented a type of familial cardiomegaly.[7] Furthermore, in the long course of each patient, competent medical care had failed to record evidence of systemic hypertension at any time. Minimal thickening of the mitral valve leaflets and smooth nodulation of the edges, with some thickening of the chordae tendineae, led the pathologist to report the presence of inactive rheumatic valvulitis in each case, but admittedly this appeared to be inadequate to explain the extreme degree of muscular hypertrophy. Similarly, both of Morrow's cases had mitral insufficiency which was thought to be inadequate to produce such severe ventricular changes.[3] His cases likewise showed left atrial pressure pulses which were normal in contour, as was true in our Case 2. One might surmise that the extremely high intraventricular pressures attained during

isotonic contraction of the left ventricle led ultimately to the pathologic tear in the anterior mitral leaflet which was observed in Case 2 at the time of surgery. The absence of cardiac dilatation and intractible congestive phenomenon are distinctly unusual for idiopathic ventricular hypertrophy, although embolization, a feature common in the latter entity, was found in both cases. However, according to the review by Spodick,[8] only a small minority of cases of idiopathic ventricular hypertrophy disguise themselves as valvular heart disease. In addition, the presence of hypertrophy involving both chambers in the absence of anatomic obstruction to the pulmonic as well as the systemic circulation suggests that primary myocardial hypertrophy of both ventricles existed in each case. It is noteworthy that all of the reports to date have remarked on the ventricular hypertrophy being so massive that the ventricular cavities were reduced to a minimal size. The symmetrical nature of this hypertrophy in one of Morrow's cases even afforded a physiologic explanation for the demonstration of subvalvular stenosis in the right ventricular outflow tract which was observed at right heart catheterization. Possibly, Dr. Paul Wood's suggestion that we classify all of these cases as cardiomyopathies of uncertain origin is, after all, the most reasonable.[9]

SUMMARY

Two cases of functional subaortic stenosis due to cardiomyopathy of uncertain origin are reported. Attention is directed to the close clinical similarity with organic aortic stenosis. The useful and specific diagnostic character of the direct brachial arterial pulse tracing in this differential is emphasized. The poor tolerance of these patients for any attempt at surgical correction makes their clinical recognition mandatory.

The authors wish to express appreciation to Dr. Earle Kay and Dr. Henry Zimmerman, of Cleveland, Ohio, for making available their findings in Case 1. Likewise, special thanks are due to Dr. Paul Wood, of London, England, for his personal interest and helpful suggestions regarding Case 2.

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Multifocal Ventricular Extrasystoles With Adams-Stokes Syndrome in Siblings

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Ventricular extrasystoles of multifocal origin are usually observed in patients with organic heart disease. They may lead to ventricular tachycardia or fibrillation, and the prognosis is therefore doubtful.[16] Little is known about the significance of hereditary factors in extrasystoles,[9,12] and no description of a familial occurrence of multifocal extrasystoles has been found in the available literature.

This paper presents the cases of three sisters who suffered from frequent attacks of multifocal ventricular extrasystoles, but who had no signs of organic heart disease. Two of the patients also had Adams-Stokes syndrome, and one of them died suddenly. The parents, who were unrelated, and two other siblings had no arrhythmia, and electrocardiograms recorded on them were normal.

CASE REPORTS

CASE 1.—A. H. was born in 1935. In 1942, the patient was hospitalized as a carrier of diphtheria bacilli. Apart from this she had no disease of importance. A few months later she was examined by the school physician and an irregular pulse was observed.

In 1949, she had her first syncopal attack. She fainted while bicycling and was treated for concussion of the brain in another hospital. The pulse was recorded to be irregular.

During the years 1949 to 1957, she had an average of two to three syncopal attacks per year. She felt prodromal symptoms of tiredness and malaise for several hours. The duration of the attacks varied from seconds up to several minutes. During the attacks she was unconscious and sometimes had convulsions, was incontinent of urine, and had frothy discharge from the mouth. The attacks sometimes occurred after emotional excitement, but seemed to be independent of exertion. Between the attacks she often had unpleasant sensations caused by numerous extrasystoles, especially during menstruation and periods of constipation. She never had other heart complaints.

From 1957 onward the attacks increased in frequency and severity, and in 1958, she was admitted to the hospital for observation. At that time she was a 23-year-old woman of healthy appearance, but rather psycholabile. The height was 158 cm., and weight was 55 kilograms. The blood pressure was 120/80 mm. Hg. The physical examination revealed no organic heart disease. X-ray examination showed a heart shadow of normal size and shape. The electroencephalogram was normal. Venous pressure and circulation time (Decholin), basal metabolic rate, glucose tolerance test, serum potassium, sodium, calcium and phosphorous were also within normal values.

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The heart rhythm was usually irregular because of frequent extrasystoles. At intervals, pulsus bigeminus, pulsus trigeminus, or runs of extrasystoles were observed (Fig. 1). The arrhythmia increased after exertion.

In the hospital she had three syncopal attacks, one of which I observed. This attack lasted for 2 to 3 minutes. The patient became unconscious, with marked pallor and twitching in the arms and legs, but without cyanosis. On auscultation, a very rapid irregular heart action was observed at first, probably runs of extrasystoles. Later on no heart sounds could be heard, nor could any pulse be felt for 20 to 30 seconds. Finally, sinus rhythm returned (Fig. 2), and the patient immediately recovered.

On repeated follow-up examinations, multifocal ventricular extrasystoles were always registered, with only short periods of regular sinus rhythm. Quinidine and procaine amide in large doses reduced the number of extrasystoles to some extent, and during this period of treatment she was free from syncopal attacks for 7 months. Treatment with digitalis, reserpine, meprobamate, phentolamine, atropine, and potassium had no definite effect.

Case 2.—L. H. was born in 1932. As a child she had scarlet fever, but no other important diseases. From the age of 8 years she had syncopal attacks, and from the age of 10 years she also had convulsions and was incontinent of urine during the attacks. Premature beats were first observed at this time. In 1944, attacks occurred frequently, and she was admitted to the hospital for observation.

The physical examination revealed no signs of organic heart disease. Frequent paroxysms of ventricular extrasystoles were observed, with a heart rate of about 140 per minute (Fig. 3).

After discharge she was free from syncopal attacks for 7 years and even took part in sports. In 1951, she suddenly cellapsed while bicycling and died instantaneously. No autopsy was performed.

Case 3.—B. H. was born in 1940. At the age of 2½ years the girl had a mild diphtheria, without complications. She never complained of heart symptoms. At the age of 14 years she was examined by the school physician, and extrasystoles were observed.

The patient was thereafter examined three times by an internist. Numerous ventricular extrasystoles were registered upon each examination (Fig. 4). No other signs of heart disease were revealed, and the patient had no syncopal attacks.

DISCUSSION

Three out of five siblings were observed to suffer from multifocal ventricular extrasystoles without any other signs of organic heart disease. In two of the children the arrhythmia was accompanied by Adams-Stokes syndrome. One of them died suddenly. The other was observed during an attack of unconsciousness. At the beginning of the attack the heart action was rapid and irregular. During the syncope, heart sounds could not be heard nor could any pulse be felt for a period of 20 to 30 seconds. After the attack a normal sinus rhythm was registered. Ventricular tachycardia or ventricular fibrillation is the most probable cause of the Adams-Stokes seizures.

There are two interesting points regarding these cases: first, the familial occurrence, and secondly, the Adams-Stokes attacks caused by the extrasystolic arrhythmia without any other signs of organic heart disease. As to the familial occurrence, this is no rarity in congenital heart diseases. Carleton and associates[1] collected a series of 141 families in which two or more members were affected, most of them with complicated malformations.

Gyurov and Pantev[4] described three brothers and one sister in whom atrioventricular conduction disturbances were present in three and nodal extrasystoles in the fourth. One of them died suddenly, and another had attacks of Adams-Stokes type.

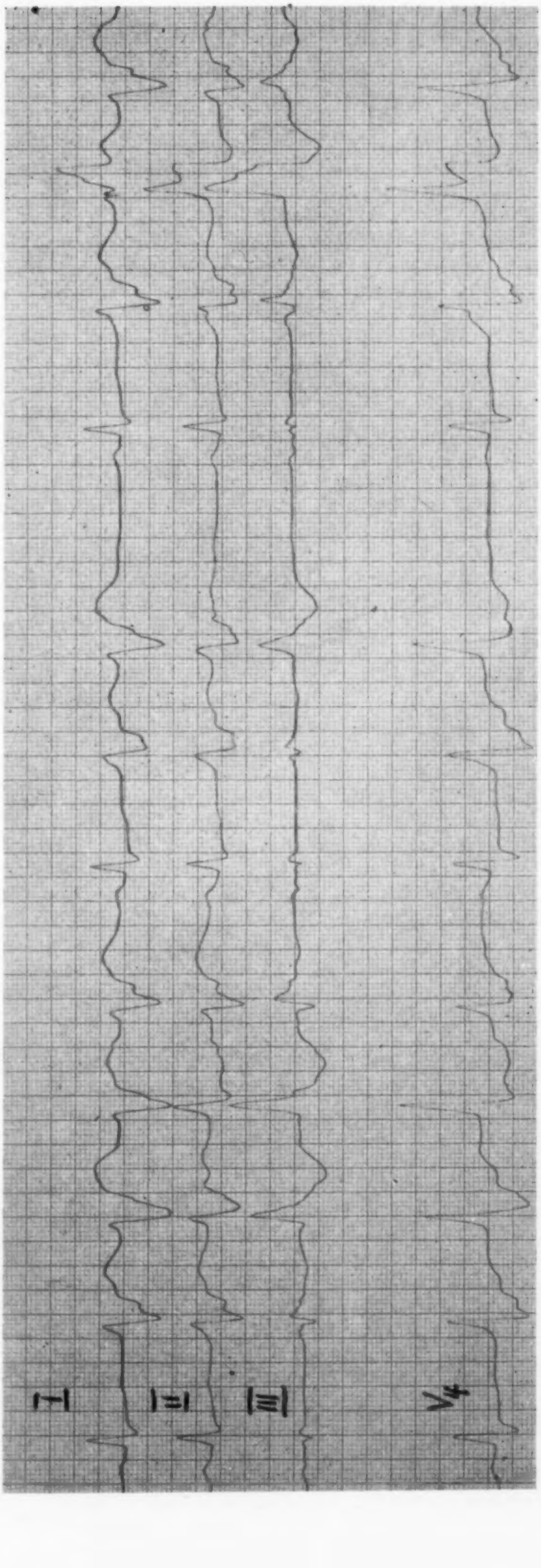

Fig. 1.—Case 1. Electrocardiogram recorded on Oct. 22, 1958. Leads I, II, III, and V_4. Frequent ventricular extrasystoles of various forms.

Sudden heart death has also been observed in siblings with Marfan's syndrome (Taschen[15]). Jervell and Lange-Nielsen[6] mention sudden death in three siblings with congenital deaf-mutism and prolonged Q-T interval.

Cases of ventricular tachycardia and ventricular fibrillation resulting in Adams-Stokes seizures have also been published with increasing frequency in recent years.[2,5,10,14] It is also established that extrasystoles which occur early in diastole, in the so-called "vulnerable period," may initiate ventricular fibrillation (Scherf[11]). Levine[8] considers that sudden death due to emotional trauma may be explained in this manner. Schmidt[13] reports cases in which extrasystoles early in diastole are forerunners of Adams-Stokes seizures.

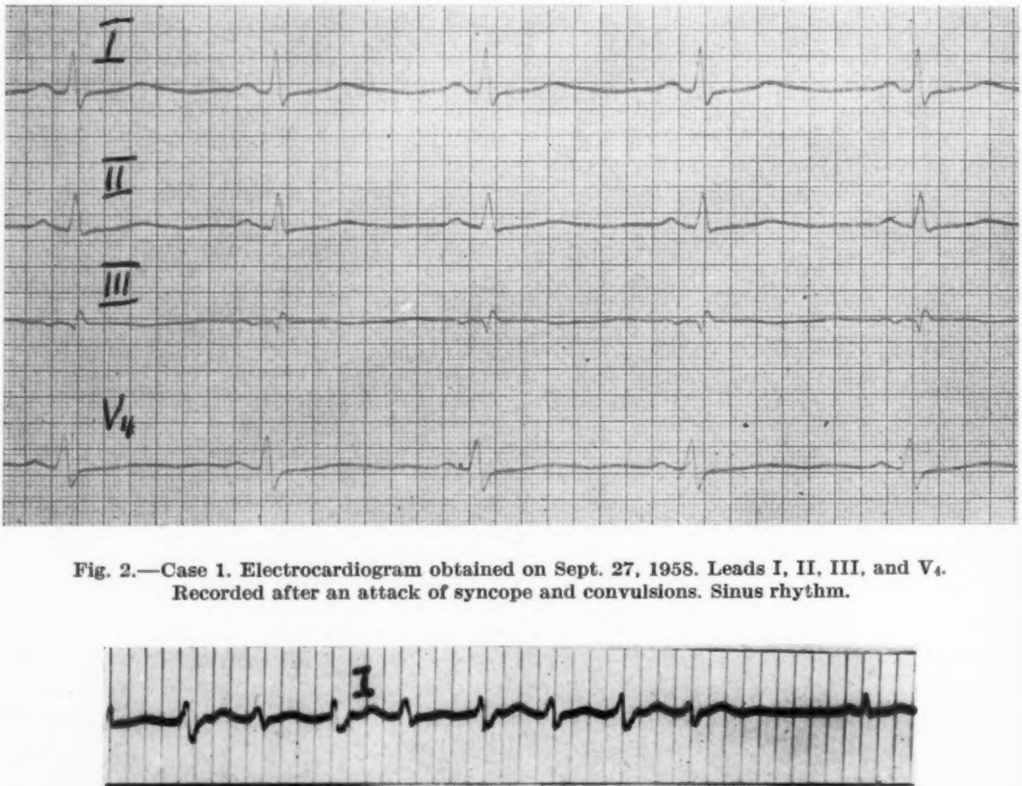

Fig. 2.—Case 1. Electrocardiogram obtained on Sept. 27, 1958. Leads I, II, III, and V_4. Recorded after an attack of syncope and convulsions. Sinus rhythm.

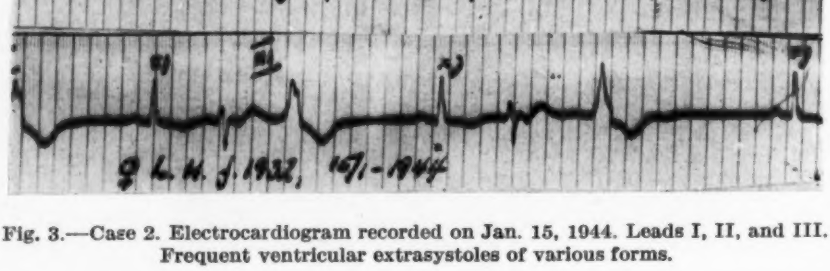

Fig. 3.—Case 2. Electrocardiogram recorded on Jan. 15, 1944. Leads I, II, and III. Frequent ventricular extrasystoles of various forms.

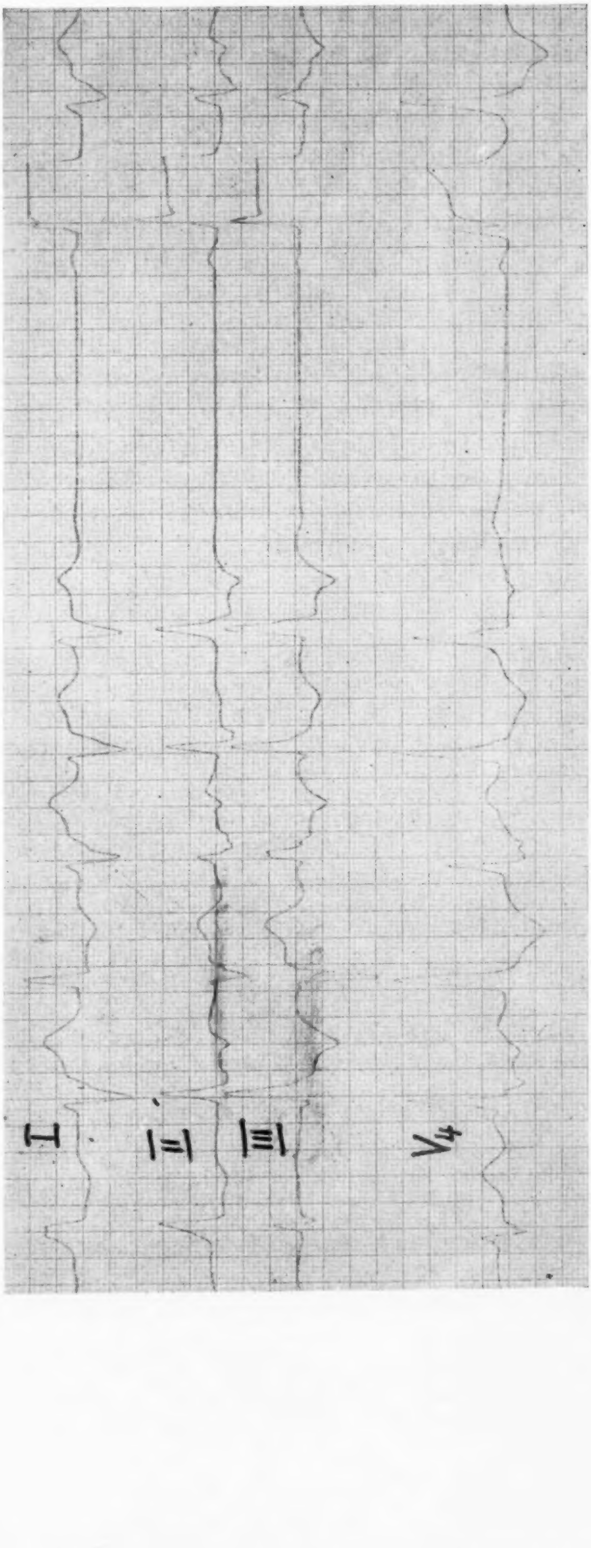

Fig. 4.—Case 3. Electrocardiogram recorded on Oct. 13, 1958. Leads I, II, III, and V_4. Frequent ventricular extrasystoles of various forms.

Froment, Gallavardin and Cahen[3] describe a well-defined group of patients, usually young people, with otherwise normal hearts, who have almost permanent extrasystolic arrhythmia, interrupted by attacks of paroxysmal ventricular tachycardia, very resistant to therapy. Among these patients, Adams-Stokes seizures may also occur.[7] The authors[3] report two patients suffering from this tendency of arrhythmia who were observed for 35 and 24 years.

Our cases seem to belong to this Froment type of extrasystolic arrhythmia. The familial occurrence is remarkable, however, and in the available literature no similar observations have been mentioned.

Concerning the etiology, nothing can be said with certainty. One probably has to do with a congenital disorder of the myocardial metabolism, but of quite unknown nature.

SUMMARY

A familial appearance of multifocal ventricular extrasystoles without other signs of heart disease has been mentioned. In two of the three sisters, Adams-Stokes seizures occurred, and one of them died suddenly. The immediate cause of these attacks is believed to be ventricular tachycardia or ventricular fibrillation. The etiology of the condition is quite unknown. A congenital disorder of the myocardial metabolism may be presumed.

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The Electrocardiogram in Acute Arsenic Poisoning

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The poisonous uses of arsenic, known since antiquity, have made the drug a favorite among those bent on destruction, self and otherwise. Its therapeutic effects were known to the Greeks and Romans but perhaps achieved greatest prominence in the prepenicillin treatment of syphilis. Present therapeutic value is limited, but widespread use for killing rodents and insects persists. For this reason, arsenic is readily available and constitutes a major source of danger in accidental, suicidal, and homicidal ingestion. Arsenic, indeed, is said to be the most common source of acute heavy metal poisoning.[1] Its toxic effects on the gastrointestinal tract, the central nervous system, the blood-forming organs, and the kidneys are well known, both clinically and pathologically. However, textbooks of cardiology and internal medicine make only fleeting reference to the effect of arsenic on the heart and electrocardiogram.[2-5] Although cardiovascular collapse may occur, heavy metal damage to the heart is said to be rare[6] and is not generally emphasized in discussions of arsenic toxicity.[7,8] Sporadic reports appear in the literature describing T-wave abnormalities, particularly in cases of chronic arsenic intoxication.[9-13] A search of the literature revealed no recording of serial electrocardiograms taken throughout the course of acute arsenic poisoning, including recovery and remote follow-up. A recent clinical experience illustrates the profound, though reversible, effect which arsenic can have on the electrocardiogram.

CASE REPORT

The patient, a 22-year-old Negro woman, entered the Miami Valley Hospital at 3:47 P.M. on Oct. 2, 1954, stating that she had taken approximately one-half teaspoon of rat poisoning at 12:00 noon on the day of admission. This material was later found to contain 97 per cent arsenic trioxide (As_2O_3). The patient was vomiting clear liquid material and complaining of epigastric pain. Immediately upon admission, gastric lavage was performed with saline and magnesium sulfate. Two ounces of olive oil were given orally. The patient continued to vomit. The blood pressure was 98/58 mm. Hg, and the pulse was 100 and regular. The patient walked to the lavatory

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and collapsed. Her temperature was 100° F. orally. An intravenous infusion of 10 per cent glucose and water was begun. At 8:00 P.M., the contents of the poison were learned, and the patient was given 1.8 c.c. of a 10 per cent solution of 2, 3-dimercaptopropanol (British antilewisite, BAL) intramuscularly. This was calculated on a basis of 3 mg. per kilogram of body weight. The patient continued to complain of upper abdominal cramping pain and was given morphine sulfate, 1/6 grain, and atropine sulfate, 1/150 grain, by hypodermic injection. The second dose of BAL (1.8 c.c.) was given intramuscularly at 9:00 P.M. The intravenous infusion was continued with glucose and saline, and a Levin tube was passed, with continuous suction. BAL was given in doses of 2 c.c. (10 per cent solution) every 4 hours beginning at 1:00 A.M. on the morning after admission. On the day after admission, nausea continued and the patient vomited some 300 c.c. of a dark bile-like material.

Considerable tenderness in the lower abdominal quadrants now became more apparent, and pelvic examination suggested the presence of inflammatory disease. This process, apparently unrelated to the ingestion of arsenic, caused some difficulty in the evaluation of the abdominal complaints. Penicillin was started. The blood pressure was 110/70 mm. Hg. The pulse was 100 and regular. Physical examination revealed only moderate toxicity. The fundi were within normal limits. There was no facial asymmetry. The lung fields were clear. Examination of the heart revealed a soft blowing Grade 1 apical systolic murmur. Deep reflexes were physiologic. No neurological defect was noted. There was no edema. Peripheral pulses were intact. There was no adenopathy. Urine output was not decreased. Urine specific gravity was 1.020. One-plus albumin was present. Many red cells and white cells were seen.

Laboratory data on admission showed 3.9 million red cells, with 14,850 white cells. The hemoglobin was 12 Gm. per cent. The differential smear included 88 polymorphonuclear leukocytes and 12 lymphocytes. On the second hospital day the white blood cell count had fallen to 7,750, with 72 per cent polymorphonuclear leukocytes. Urinalysis now revealed only a trace of albumin, with no red cells and a few white cells. The blood urea nitrogen was 14.2 mg. per cent. The serum chlorides were 98 mEq./liter, serum sodium was 138 mEq./liter, and the CO_2 combining power was 46 volumes per cent. On the following day the urinary findings were unchanged. The serum electrolytes were also not changed. The serum potassium, which had been inadvertently omitted from the first electrolyte profile, was 4.3 mEq./liter.

On the third hospital day the physical findings were essentially unchanged. Abdominal distress and nausea persisted, although the patient was able to take small liquid feedings. Pro-banthine, in intramuscular doses of 15 mg. every 6 hours, had seemed to relieve the nausea. BAL was continued in doses of 2 c.c. every 4 hours until the night of the third hospital day, when it was reduced to every 6 hours. At 10:00 P.M. on the third hospital day the patient became agitated and difficult to manage. On the fourth hospital day she became totally uncooperative and had to be transferred to the psychiatric division. She became violent and required physical restraint and sedation. On the fifth hospital day the BAL was reduced to doses of 2 c.c. every 12 hours. On the twelfth hospital day this medication was discontinued. After several days of violent behavior with delusional manifestations of a paranoid character, the patient gradually resumed a rational state. During hospitalization there was no rise in the blood urea nitrogen. The electrolyte profile remained within normal limits. On the eleventh hospital day a trace of arsenic was still present in the urine. On the seventeenth hospital day, the patient was able to be discharged from the hospital. At this time she was free of all physical complaints, except that a generalized skin eruption characteristic of that seen in arsenic intoxication began to appear.

On the night of admission a 12-lead electrocardiogram was taken (Fig. 1). Nonspecific T-wave changes were noted in the limb leads and in all precordial leads. Serial tracings revealed marked improvement by the eighth hospital day, and a return to a normal contour by the fourteenth hospital day. No prolongation of the Q-T interval occurred. There was no S-T-T segment deviation nor was the QRS complex altered. The patient was not seen again until some 25 months after the ingestion of the arsenic, at which time she was entirely free of symptoms and findings. A standard 6-foot chest film was within normal limits. No murmur was heard. An entirely normal electrocardiogram was seen.

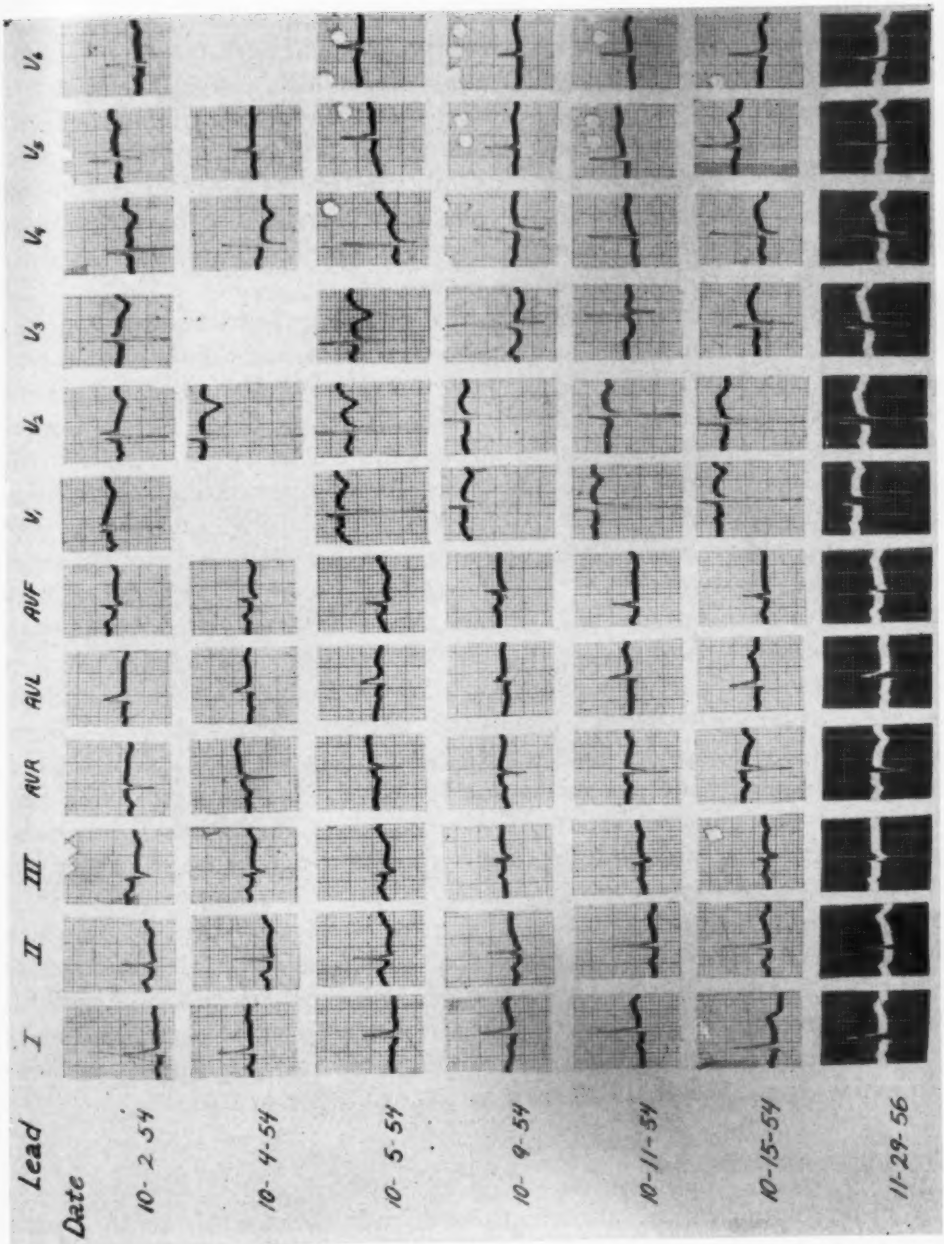

Fig. 1.—Serial tracings illustrate the electrocardiographic evolution in arsenic intoxication. The first tracing was taken approximately 8 hours after ingestion of arsenic.

COMMENT

The present case is interesting in that a rather striking T-wave evolution occurs in the presence of a relatively mild systemic reaction, marked primarily by gastrointestinal manifestations. It is difficult to evaluate the role of arsenic in the production of the emotional reaction. The instability of the T wave and the many factors which may influence it are well known and need not be recounted at this time.[14] The nonspecificity of T-wave changes has been emphasized in a previous communication.[15] The mechanism by which arsenic induces the T-wave changes is not known. Arsenic is known to produce capillary damage, with dilatation and changes in the permeability of the vessel walls. The effect of arsenic on the electrocardiogram, therefore, may be mediated through damage to vascular structures or may be due to direct myocardial injury. The inference in this instance is that no lasting damage occurred.

The findings in the case presented are consistent with the results described by Butzengeiger[10] in human beings and by Massman and Opitz[16] in experimental animals. The latter authors gave progressively increasing doses of arsenic to cats and took electrocardiograms at 7-day intervals. They found T-wave changes in the form of flattening and inversion. They considered the contour to be similar to that seen in myocardial infarction. In most instances, prolongation of the Q-T interval was seen, but in a few cases there was shortening. QRS changes included splintering of the complexes and low voltage. There was no defect in impulse formation or in A-V conduction. No intraventricular block was seen. The electrocardiographic changes were inconstant and not every animal was affected. The authors postulated that the electrocardiographic changes were due to direct cellular damage rather than to secondary factors, such as anemia or electrolyte or endocrine imbalance. The level of arsenic in the blood and the electrocardiographic abnormalities were not necessarily correlated. Myocardial changes at autopsy could not be found. This reinforced the idea that the arsenic may have produced enzyme inhibition. The impression was also gained that if the drug were stopped prior to lethal dosage, the effects on the cardiovascular system were reversible.

It is noted that the pathophysiology of arsine (AsH_3) intoxication (in which T-wave changes have also been described) is quite different from that of arsenous oxide poisoning.[19] Arsine is a highly toxic gas which produces red cell hemolysis and leads to hemoglobinemia, hemoglobinuria, proteinuria, collpase, and early death. The picture is that of acute renal tubular necrosis and, unlike arsenous oxide poisoning, is not favorably affected by the exhibition of BAL.

SUMMARY AND CONCLUSIONS

The electrocardiographic abnormalities in an instance of acute arsenic intoxication are described. The evolution is traced from the appearance of nonspecific T-wave abnormalities several hours after ingestion of the arsenic until a normal pattern had reappeared some 14 days later. The normal contour was still present some 25 months later, and there was no suggestion of disease of the cardiovascular system. The evidence suggests that greater attention be paid

to the effect of arsenic on the cardiovascular system. Further elucidation of the mechanism of action of arsenic may help to solve the enigma of the T-wave and the repolarization process.

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Review

Depressor Polypeptides

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INTRODUCTION

In recent years there has been an increased interest in pharmacologically active polypeptides obtained from different tissues and organ systems. The identification of each polypeptide as a separate and distinct substance from those previously described has not been an easy task. In this regard, then, one is immediately overwhelmed by the number of different substances, presumably of polypeptide nature, which have been reported in the literature. For example, the following pharmacologically active substances have been reported: bradykinin,[1-3] kallikrein (Padutin),[4-6] kallidin,[6] substance U,[7,8] substance P,[9-11] pain-producing substances (PPS),[16] wasp kinin,[20,21] clostridin,[22] colostrokinin,[23] pepsitensin,[24] pepsitocin,[24] angiotensin I and II,[25-30] renin,[26,31-34] anephrotensin,[35] substance A,[36,37] and finally those of the neurohypophysis, vasopressin and oxytocin.[38-40] Earlier work on pharmacologically active polypeptides has been reviewed by Gaddum,[41] Werle,[5] Pernow,[42] Rocha e Silva,[43] and Rigler.[44] An important account of current research in this field may be found in a book edited by Schachter.[45]

Work in several laboratories has indicated that vasodepressor polypeptides seem to be involved in the control of the vascular system under physiologic as well as pathologic conditions.[46-49] Thus, it has become necessary to understand the conditions through which they may regulate the circulation, the mechanisms of their formation and destruction, and their possible role in various homeostatic mechanisms of the body. In a review such as this it would be impossible to cover in detail the pharmacologic aspects of all the active polypeptides. Therefore, we propose to approach the pharmacology of the vasodepressor polypeptides by using bradykinin as the model substance. The other active substances will then be discussed with reference to their differences and similarities to the model polypeptide.

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A. BRADYKININ

In 1948, Rocha e Silva and his associates[1] were experimenting with the pharmacologic action of the venom of *Bothrops jararaca* and found that perfusion fluid (defibrinated blood) taken from a dog which was being perfused through the portal vein immediately after injection with the venom stimulated a contraction of an isolated guinea-pig ileum. This occurred even after the gut had been desensitized to the venom and no longer reacted to it. When the venom was incubated with the blood for a few minutes in vitro, the effect on the isolated gut was even more pronounced. Rocha e Silva postulated that the venom released a smooth-muscle stimulant from the blood that was responsible for the contraction of the gut. This substance was found to be distinct from other known, naturally occurring compounds, and was given the name ***bradykinin*** because of the delayed, slow contraction which it elicited on the guinea-pig ileum. In addition to its stimulating effect on smooth muscle it also produces a vasodilatation which leads to a depressor response.

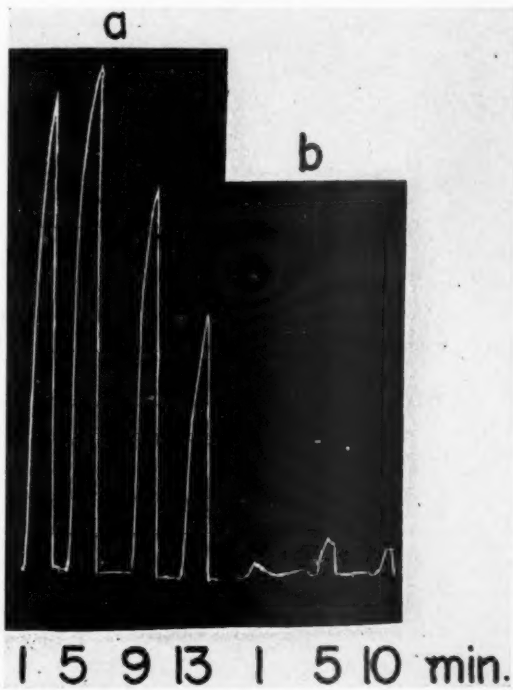

Fig. 1.—Contractile responses of an isolated guinea-pig ileum to 0.2 ml. aliquots of an incubation mixture of crystalline trypsin and fraction IV-4. In panel *a*, aliquots were added after various incubation times, showing the time-course formation of bradykinin, with a maximum formation between 2 and 5 minutes of incubation. Panel *b* illustrates a duplicate experiment except that crystalline soy-bean trypsin inhibitor was added to the incubation mixture, resulting in an inhibition of the formation of bradykinin.

1. *Formation.*—Various investigators[1-3,17] have shown that the active material, bradykinin, is released from its precursor by proteolytic enzymes, such as trypsin (see Fig. 1), plasmin, or similar esterolytic enzymes, which are present in snake venoms. Since bradykinin is indistinguishable from kallidin[21,50] by phar-

macologic methods, perhaps one can also add the different kallikreins to the list of enzymes that form bradykinin. In the early work on bradykinin, it was quite clear to Rocha e Silva and his colleagues that this substance was a polypeptide. First, it could be formed by the actions of proteolytic enzymes (trypsin, venom of *Bothrops jararaca* or *Agkistrodon piscivorus*) on plasma globulin, and secondly, it was destroyed by proteolytic enzymes, such as chymotrypsin and those found in the venom itself. The precursor of bradykinin is contained in the α^2-globulin fraction of normal plasma and has been given the name ***bradykininogen***.[1] This fraction could be dialyzed, boiled with acetic acid, or precipitated with alcohol without releasing the active material or affecting the enzymatic release of the active material.[1,51] However, Rocha e Silva and Holzhacker[52] have recently reported that if fresh rat plasma was boiled for 1 to 10 minutes in $0.1N$ hydrochloric acid, neutralized to pH 7 and incubated at 37°C., a spontaneous release of bradykinin occurred, as measured on the guinea-pig ileum. It is of interest[53] that the same globulin fraction that contains bradykininogen also contains the precursor of angiotensin. In fact, the precursors may be within a single protein, since if one produces angiotensin by incubation of protein precursor with renin, no bradykinin could be produced upon subsequent incubation with trypsin.

Rocha e Silva and his colleagues have reported several procedures for the purification of bradykinin. The activity of bradykinin is usually expressed in units.[1,54] A unit has been arbitrarily defined as the activity contained in 1 milligram of the first homogenized material (Pool 1). Simple precipitation with several volumes of ethyl ether from glacial acetic acid produces a product containing 3 to 6 units per milligram.[54] A second procedure consists of column chromatography in which a cellulose (paper pulp) column is used; the material obtained by this procedure represents an activity of 10 to 20 units per milligram.[55] Column chromatography in which aluminum oxide is used, prepared according to Brockman, can effect a purification some 50 times that of the original preparation.[54] A preparation which contained approximately 1,200 units per milligram[55,56] could be obtained by combining the cellulose column with the aluminum-oxide column. Andrade and Rocha e Silva[56] have reported that a preparation which contained 5,000 units per milligram could be obtained by using an ion-exchange resin, Amberlite, IRC-50. All attempts for large-scale preparative methods with high activity were not successful; however, Hamberg and Deutsch[57] reported a method for the large-scale preparation of bradykinin with a relatively low degree of activity. Recently, Elliott, Lewis and Horton[58,59] have succeeded in preparing a pure bradykinin and have reported that the peptide on acid hydrolysis yielded serine, glycine, proline, phenylalanine, and arginine in the molar proportions 1:1:3:2:2. The pure peptide was obtained by using the following procedures in succession; countercurrent distribution, elution chromatography on two successive carboxymethylcellulose columns, and, finally, preparative paper electrophoresis. According to the report of Elliott, Lewis and Horton,[59] and the synthetic work of Boissonnas[60] and his collaborators, the sequence of amino acids in the pure peptide is: arginine: proline: proline: glycine: phenyl-

alanine: serine: proline: phenylalanine: arginine. Thus, it is not too surprising that bradykinin has such a high isoelectric point,[67] since the basic amino acid, arginine, represents 25 per cent of the molecule.

2. *Destruction*.—Since the pharmacologic response to bradykinin appears to require an intact polypeptide, there have been numerous studies carried out on factors which control the inactivation of this polypeptide. Incubation with chymotrypsin leads to inactivation, whereas trypsin and pepsin have no effect.[61] Prolonged boiling in concentrated hydrochloric acid inactivates it,[62] whereas it resists long boiling in $1.0N$ hydrochloric acid.[1] It is rapidly destroyed by boiling in $0.1N$ sodium hydroxide.[1] The plasma, as well as the purified globulin fractions, contain enzymes, probably peptidases, which destroy bradykinin.[61,63] In addition, there is an enzyme in the cortex of the kidney which also destroys bradykinin.[63] That this activity is not due to natural cathepsins was shown by Rocha e Silva,[3] who reported that the bradykininolytic activity of kidney has a pH optimum around 7.4, is inhibitied by cysteine, and is completely inactive at pH 5 where the natural cathepsins of the tissues have their optimum of activity. It is of interest that the destruction of bradykinin can be prevented by previously boiling the substrate in the presence of acetic acid,[53] heating at 37°C. in $0.1N$ hydrochloric acid,[58] or by carrying out the incubation under anaerobic conditions in the presence of cysteine.[57] The snake venoms vary in their content of bradykininolytic activity. The venom of *Bothrops jararaca* has strong bradykininolytic activity, whereas the venom of *Agkistrodon piscivorous* has no bradykinin-destroying activity.[64]

3. *Circulatory Action*.—One of the predominant pharmacologic properties of bradykinin is its vasodilator activity, which produces a fall in blood pressure in all species studied: rabbit,[3] cat,[65,66] dog,[65] chicken,[65] rat,[67] and guinea pig[67] (see Fig. 2). The vasodepressor effect is insensitive to atropine or to antihistaminics.[3] It has been generally assumed that the effects of bradykinin on the circulatory system are peripheral, since it produces a vasodilation when injected intra-arterially into the ear of rabbits[68] or into the region of the submandibular salivary gland of the cat.[69,70] The rat is very sensitive to bradykinin, and a few units injected intravenously will produce a pronounced fall in blood pressure that will persist for a long period.[67] Similarly, rabbits are also sensitive to bradykinin, since 150 units of the purest bradykinin (5 units per microgram) will produce a profound drop in blood pressure that persists for over an hour.[67] In the guinea pig, 15 to 20 units intravenously often produces death after coma which may last for as long as 1 hour. According to Rocha e Silva,[43] death is apparently due to a prolonged and irreversible fall in blood pressure. The time required for the blood pressure to return to normal level after a pronounced and persistent vasodepressor dose of bradykinin has been given is much longer than it is conceivable for bradykinin to withstand destruction by the bradykinin-destroying enzymes of plasma. Thus, it would seem that once bradykinin is bound to the tissue receptors, it becomes more resistant to the inactivating enzymes. The anesthetized rat can be made much more sensitive to bradykinin if the animal is adrenalectomized a few days before intravenous injection of the challenging dose of bradykinin.[67]

Rocha e Silva and associates[66] have studied the vasodilator effects of bradykinin in cats in relation to previous injections of common hypotensive drugs. The pharmacologic agents used were: (a) a sympatholytic (phenoxybenzamine), (b) a gangliolytic (hexamethonium), and (c) centrally acting drugs (hydralazine, chlorpromazine, and reserpine). The centrally acting agents and the sympatholytic drug strongly delayed recovery from hypotension provoked by a standard dose (25 to 30 units) of bradykinin given intravenously. The gangliolytic agent, hexamethonium, had no potentiating effect, whereas cocaine had the opposite effect in shortening the time of recovery after an injected dose of bradykinin.

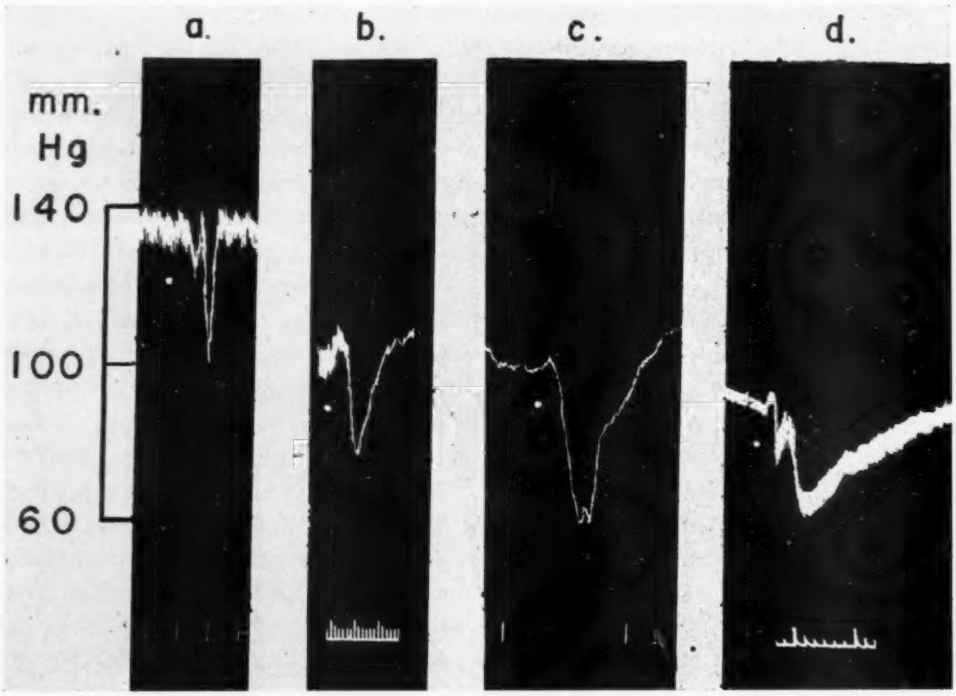

Fig. 2.—Vasodepressor effects of bradykinin in various species. Mean blood pressure is given in mm. Hg. Administration of intravenous doses is indicated by white dots. The time interval in panels *a* and *c* is 1 minute, and in panels *b* and *d* it is 10 seconds. *a*, Blood pressure in dog. *b*, Blood pressure in cat. *c*, Blood pressure in chicken. *d*, Blood pressure in rabbit. This illustrates the effects of relatively small doses of bradykinin. Larger doses tended to produce a sustained hypotensive response.

In an effort to determine whether bradykinin has an effect centrally, Rocha e Silva and associates[66] injected bradykinin into the lateral ventricles of anesthetized cats. The effect of a small dose of bradykinin which would produce only a transient fall if given intravenously was more presistent and slow in onset when given by the central route. There was a definite stimulation of respiration after the injection. Although these data would indicate that bradykinin provokes a vasodepressor activity via a central component, one wonders whether enzymatically destroyed bradykinin would be inactive. The potentiation of the hypotensive effect of bradykinin observed with sympatholytic or centrally acting agents, such as reserpine, might be explained on the basis that the return of the

blood pressure to normal level was impaired by the blockade of the peripheral sympathetic receptors at the walls of the blood vessels or by depletion of the stores of peripheral catecholamines. However, one should not at the same time ignore the possibility that the central component might also influence the course of the hypotensive response to bradykinin.

Bradykinin has no significant effect upon the isolated perfused rabbit heart,[3] and even when injected intravenously there is no evidence of its working through any cardiac mechanism. In addition, Rocha e Silva[43] reports that bradykinin has no gangliolytic or sympatholytic effect. Holdstock and associates[21] have compared the effects of bradykinin, kallidin, wasp kinin, and histamine on capillary permeability in the skin of guinea pigs. Using the increase in capillary permeability to circulating pontamine blue as a measure of activity, they found that bradykinin, kallidin, and wasp kinin were indistinguishable pharmacologically in their ability to increase capillary permeability; however, wasp kinin was more potent in this respect when equivalent concentrations were used, as measured on the guinea-pig ileum. The kinins were found to be more effective than histamine in causing increased permeability to pontamine blue in the guinea pig and the rabbit.

4. *Action on Smooth Muscle.*—Bradykinin posseses a powerful stimulating effect upon the smooth muscle of the guinea-pig ileum, rabbit intestine, rat uterus, rat stomach, and rat ileum.[1,14,41] The smooth muscle of the rat duodenum and rat colon, unlike most smooth muscle, is relaxed in the presence of bradykinin.[14,71] Bradykinin has been found to be very active on the intestine of the cat,[67] only slightly active upon the rectal cecum of the hen,[72] and inactive on carotid arterial strips which were spirally cut.[65] The stimulating action of bradykinin upon the smooth muscle of the guinea pig is resistant to atropine, to antihistamines, and to paralyzing concentrations of nicotine.[65,73] Paton[74] has described a slight and possibly significant antagonistic effect of compound 48/80 toward the stimulating effect of bradykinin on smooth muscle. TEA in fairly large doses potentiated the

TABLE I. SOME PROPERTIES OF VASODEPRESSOR POLYPEPTIDES

	DEPRESSOR EFFECT	STIMULATE INTESTINE AND UTERUS	SOURCE	FORMED BY	DESTROYED BY		
					CHYMOTRYPSIN	TRYPSIN	PEPSIN
Bradykinin	+	+	Plasma protein	Trypsin, snake venom	+	0	0
Kallidin	+	+	Plasma protein	Kallikrein	+	0	0
Plasma kinin	+	+	Blood	Plasmin	+	0	—
Substance Z	+	+	Urine	—	+	0	0
Wasp kinin	+	+	Wasp venom	—	+	+	—
Clostridin	+	+	Plasma protein	Clostridium histolyticum (protease)	+	0	0
Clostridin	+	+	Colostrum	Saliva	+	0	0
Substance P	+	+	Brain and gastrointestinal tract	—	+	+	+

bradykinin contraction on the guinea-pig ileum and rat uterus.[75] The potentiation is resistant to atropine and is probably a direct action on the muscle and not related to the gangliolytic properties of TEA. (See Table I.)

Bradykinin can be easily distinguished from the polypeptides angiotensin, oxytocin, vasopressin, pepsitensin, substance A, and substance P, by parallel assay, enzymatic destruction, and inactivation by thioglycollate.[14,25,37,38,65,71] It has not been possible to distinguish bradykinin from substance Z, kallidin, the plasma kinins, and urinary kinins.[14,17,21,50,71] Gaddum and Horton[14] have concluded that the same active principle may be responsible for the biologic activity of bradykinin, substance Z, glass-activated kinin, and kallidin; however, the final proof must come by chemical analysis of the pure polypeptides.

5. Physiologic Significance.—When skeletal muscle and glandular systems are active, their blood vessels dilate and the rate of blood flow through them increases. It is quite clear that this is a very useful vascular reaction; however, the mechanisms responsible for this vasodilation have remained uncertain until recent times. Hilton and Lewis[70] detected a stable vasodilator material in the perfusate from the submandibular salivary gland of the cat. It was produced during stimulation of the chorda tympani or by injections of acetylcholine. They[46,69,70,76] believe that this material is the cause of the vasodilatation which occurs in the activated salivary gland, and that it is produced or released from the gland as a result of the activity of the gland. Furthermore, they found that the perfusate from an activated gland would produce its effects on preparations of smooth muscle, or its dilator effect in the gland, only when the perfusate was incubated with small amounts of plasma or was injected arterially into the gland after the normal supply of blood to the gland was established. It was concluded that changes which occur in the cells of the gland upon activation of the gland permit the escape into the interstitial fluid of an intracellular enzyme which acts upon the proteins present to form a vasodilator polypeptide which is very similar to bradykinin. The bradykinin thus formed will be prevented from reaching the blood by virtue of the limited permeability. It will thus produce its vasodilator effect locally and be eliminated by the lymph, either by inactivation or in the course of drainage of lymph. It is their view, then, that the hyperemia which occurs in a stimulated gland must be regarded as functional hyperemia, i.e., the vasodilatation is secondary to the activity of the glandular tissue. They suggest, furthermore, that the escape of intracellular enzymes, such as that from the submandibular salivary gland, also occurs from the cells of other organs and tissues, upon activation or injury, and that this is a basic means for the adjustment of local flow of blood for local needs.

In support of the hypothesis of Hilton and Lewis,[46] Fox and Hilton,[47] in a series of carefully controlled heat experiments on human subjects, were able to demonstrate the secretion of a bradykinin-forming enzyme in sweat collected from the forearm. The subcutaneous spaces of the human forearm were also perfused with saline. When the body was heated, the content of bradykinin in the perfusate increased up to five times the level observed when the subject was kept cool, and this increase was attributed to an increase in an enzyme from

the sweat glands reacting with the interstitial proteins. The bradykinin was postulated to be responsible for the periglandular hyperemia seen during sweating. Sweating and dilatation of the cutaneous vascular plexus are two important mechanisms which the body uses to remove excess heat. It is frequently noted that they do not occur simultaneously, a finding which has led some observers to conclude that they function under separate innervation.[77] However, with careful heat control, Fox and Hilton[47] always produced vasodilatation before sweating occurred. These data would suggest that the initiation of secretion and the initiation of vasodilatation require two different levels of nervous stimulation. At the lower level, bradykinin-forming enzyme is released, acting upon interstitial proteins to form bradykinin which provokes vasodilatation, and as the strength of stimulation is increased, sweating is initiated. This mechanism would require only one set of innervation fibers to the sweat glands, with the release of bradykinin-forming enzyme forming the basis for the local functional vasodilatation.

In view of the evidence for a relationship between the activity of the sweat glands and the active vasodilatation in human skin, it appears significant[46] that the tongue of cats and dogs is very similar to the submandibular salivary gland in that it releases bradykinin-forming enzyme after nervous stimulation. One wonders whether this system in dogs and cats is associated with functional vasodilatation as a system for the control of body heat in these species. Other secretory glands have not yet been studied in order to find out whether they produce enzymes which form bradykinin-like substances during active secretion. Werle[6] reported that kallikrein is secreted by the pancreas, and that it may be the basis for the hyperemia in the gland during secretion.

Chapman and Wolff[48] have reported studies on the neurohumoral features of the axon reflex. They perfused the subcutaneous space of the forearm with normal saline before and after the induction of the axon reflex by noxious stimulation. Aliquots of the perfusate were assayed for the ability to stimulate the isolated rat uterus or to relax the rat duodenum. A two- to threefold increase in both total volume of perfusate and its activity was observed during the axon-reflex flare, as assayed on the rat uterus. They suggest that their data support the view that a protease is liberated locally after noxious stimulation, and that this enzyme reacts with the globulin of the interstitial fluid to form a polypeptide which increases capillary permeability, lowers the pain threshold, and induces vasodilatation, edema, and other reactions relevant to the inflammatory response. These authors indicate that the polypeptide may be bradykinin; however, their implications would be more strongly supported if they had presented data which show parallel assays of the active material with standard bradykinin on two or more sensitive test systems.

6. *Relation to Various Pathophysiologic States.*—It has been shown that the vasodilator effect of bradykinin can be observed in the isolated ear of the rabbit,[68] the submandibular salivary gland and the tongue of the cat,[46] and the skin of human beings.[47] Therefore, it is conceivable that the vasodilating effect of bradykinin might explain many physiologic or pathologic phenomena involving activation of a proteolytic system in the blood or other body fluids. Chapman and Wolff[49] have carried out studies to ascertain whether and under what conditions an

enzymatic vasodilator system is present in the central nervous system. Cerebrospinal fluid was collected from subjects with (1) active disease of the central nervous system, (2) inactive, nonprogressive, or no disease of the central nervous system, (3) vascular headache of the migraine type (4) sustained nervous stimulation and pain arising from disorders of the legs or pelvic organs, and (5) disease syndromes classified as chronic schizophrenia. The fluid was bioassayed on the isolated rat uterus before (Type I response) and after (Type II response) incubation with bovine globulin. Subjects in categories 1, 3, 4, and 5 showed a positive Type II response in a significant number of instances, which would suggest the appearance in the cerebrospinal fluid of an enzyme capable of reacting with a globulin to produce a pharmacologically active substance as measured on the rat uterus and a vasodepressor reaction in the anesthetized cat. These authors[49] suggest that the polypeptide bradykinin is formed in the Type II response; however, until further proof of the character of this material is obtained, one must be cautious in evaluating it as bradykinin. They suggest that the protease-polypeptide system may be implicated in local vasomotor control within the central nervous system, and, when in excess, the components of the system may be relevant to disease.

Beraldo[19] has reported that a hypotensive substance which stimulates smooth muscle and which presents pharmacologic properties similar to those of bradykinin has been found in anaphylactic and peptone shock in dogs. If plasma globulins from a sensitized dog are placed in contact with the antigen, bradykinin is released, and also when plasma is incubated with peptone.[52] The plasminogen-plasmin system of the blood which is activated during these reactions is assumed to be the enzyme system responsible for the formation of bradykinin-like polypeptides. Therefore, bradykinin could be one of the "slowly reacting substances" released in anaphylaxis.[67] In this connection, Beraldo reports that the bradykinin found in the circulating blood of dogs during anaphylactic and peptone shock does not appear to be a very important factor in the over-all mechanism of shock; however, it may constitute an aggravating factor and may be concerned with some of the phenomena of anaphylaxis.[19] Bradykinin or a similar material has been found to be released by burning of the skin,[67] and it can be present in the fluid of the joints of rheumatic patients or in the blister fluids after burns.[16] Goodwin and Richards[78] have reported that the urine and blood of experimental animals injected with *Babesia rodhaini* and other pathogenic organisms contain substances which stimulate the isolated guinea-pig ileum and rat duodenum, and that the amount excreted rises as the infection increases. The active substances were probably polypeptides; the evidence indicated a mixture rather than a single component. It is conceivable that many traumatic episodes could possibly lead to activation of proteolytic enzyme systems with subsequent release of bradykinin. Also of interest is the report by Chapman and associates[79] that the pain of vascular headache of the migraine type may be the outcome of the combined effects of the dilatation of large arteries and the action of pain-threshold-lowering substances accumulating in blood vessel walls and perivascular tissue. These substances were defined as vasodilator polypeptides and a proteolytic enzyme.

B. KALLIKREIN (PADUTIN), KALLIDIN

In 1937, Werle, Gotze and Keppler[4] isolated from the pancreas of a dog a substance that would contract some types of smooth muscle and lower the blood pressure when injected into experimental animals. This substance of animal origin, called ***kallikrein***, has been isolated in large quantities from pancreas, pancreatic juice, salivary glands, saliva, and may also be isolated from other secretory glands.[5,6] It is found in the inactive form in blood, pancreas, and pancreatic juice, and in this inactive form is known as ***kallikreinogen***.[6] Kallikrein is excreted in both urine and feces. According to Werle,[6] the total extirpation of the pancreas of a dog results in a decrease in the amount of kallikrein appearing in the urine; the decrease is not immediate, but a maximum depression is reached within 2 weeks. He also reports that there is a decrease in kallikrein in the urine of alloxan-diabetic dogs and rabbits as well as in diabetic patients. It also appears that the level of kallikrein in the urine is dependent upon the adrenal cortex, since the amount of kallikrein in the urine is reduced in patients with Addison's disease as well as in adrenalectomized dogs. The amount of kallikrein in the urine is decreased in cases of nephritis and nephrosis.

Kallikrein is actually made up of a group of substances with similar proteolytic properties produced by various glandular systems, and it is probable that none of the kallikreins are identical.[80] They can be differentiated by various proteolytic enzymes, dilute hydrochloric acid, and the "kallikrein inactivators" found in the blood serum. They are large molecules, with a molecular weight of approximately 48,000.[6] They are nondialyzable, insoluble in organic solvents, but soluble in water or 50 per cent alcohol. Various oxidizing agents, heat, or dilute acids or alkali will destroy them. They are amphoteric, with an isoelectric point at pH 4.2.[6] They may be considered as conjugated proteins, for they are slowly decomposed by proteolytic enzymes, such as pepsin. Their pharmacologic effects are not inhibited by atropine or antihistaminics.

Kallikreins are quite potent when given by intravenous injection and will cause a drop in the mean arterial blood pressure, hyperemia of skin, muscle, lung, and brain, with a decrease in blood to the splanchnic region. According to Werle,[6] kallikrein increases the supply of blood to the coronary vessels and will cause an increase in heart beat. The amplitude of the pulse is temporarily increased, and the cardiac output per minute is transiently augmented. Kallikrein is a very potent vasodilator; however, the great blood vessels seem not to be influenced by kallikrein. The physiologic importance of kallikrein for the cardiovascular system is believed[6] to be related to the fact that it causes changes in the arterial blood supply. Werle[6] has also shown that the activity of epinephrine is blocked in anesthetized dogs if intravenous injections of epinephrine and kallikrein are given simultaneously. In addition, kallikreins will stimulate isolated strips of dog and cat intestine and also human appendix. They will not stimulate the gut of the guinea pig or uterus of the cat, rabbit or guinea pig, but will do so after incubation with plasma protein. It has been shown also that kallikrein can relax spasmodically contracted smooth muscle in the bronchi or stomach, and hat artificial cardiospasm in rabbits is relaxed by small quantities of kallikrein.[6]

Papenberg and Hensel[81] studied the action of kallikrein on the flow of blood in the muscle of man. They found that a combination of kallikrein and norepinephrine elicited a greater flow of blood in muscle than could be obtained with either agent given alone.

Probably the most important single action of kallikrein is the liberation of kallidin from its precursor, kallidinogen.[6] Kallidin is liberated from the same α^2-globulin fraction of plasma protein as is bradykinin. It is also of interest that Cohn's fraction IV-6 of plasma protein contains the precursor to kallidin.[53] Normally, after incubation of kallikrein with serum, the kallidin that is produced is quickly destroyed by serum enzymes, presumably by a peptidase and probably the aminopeptidase of the serum which is located mainly in the α^2-globulin fraction. Kallidin is produced in the circulation also when kallikrein is given by intravenous injection. It appears, then, that kallidin would account for the major portion of the action of kallikrein. Kallikrein resembles trypsin in action, but it can be distinguished in a number of ways.[6]

Kallidin is a hypotensive polypeptide of low molecular weight that is indistinguishable from bradykinin.[6,21] Proteolytic enzymes rapidly destroy its activity, especially crystalline chymotrypsin, but not crystalline trypsin. In addition to its hypotensive effect, kallidin also stimulates isolated smooth muscle, especially that of the intestine and uterus of the guinea pig. Atropine or antihistaminics do not block the effect of kallidin; however, pharmacologic activity is abolished with ninhydrin, fluorodinitrobenzene, hydroxylamine, or iodine.[6]

The physiologic function or pathologic role of kallikrein and kallidin is not known. However, almost 20 years ago, Westerfield and associates[82] injected doses of 60 mg. of purified kallikrein into dogs, and in all cases this was a fatal amount, with the dogs dying in 5 to 6 hours in extreme irreversible shock. These observations and those of the type of response seen in experimental animals after lethal radiation suggested that a connection might exist between lethal radiation and the release of kallikrein and the formation of kallidin. In this regard, Fink[83] could not demonstrate either an increased or decreased excretion of urinary kallikrein in animals which had received a lethal dose of radiation. However, since she did not report studies on blood levels, it is possible that here she might have found a change.

C. PLASMA KININS

The term ***plasma kinin,*** which is a name applied to bradykinin-like polypeptides derived from plasma proteins, was first suggested by a group of English workers at a meeting of the British Pharmacological Society in 1957.[17] It seems likely that there are several proteolytic enzymes capable of hydrolyzing the globulin fraction of plasma proteins in a similar manner, producing a group of closely related polypeptides with powerful smooth-muscle stimulating and vasodilator activity. Sources of proteolytic enzymes possessing this property include blood,[17] plasmin,[17] kallikrein,[6] saliva,[68-70] sweat,[47] cerebrospinal fluid,[49] trypsin,[3] and a protease from *Clostridium histolyticum*.[22]

Armstrong and associates[16] have reported studies on a pain-producing substance (PPS), also known as glass-activated kinin, in human inflammatory

exudates and plasma. Human inflammatory exudates, such as blister fluids, fluid of the joints in rheumatoid arthritis, pleural effusion, hydrocele fluid, and protein-rich ascitic fluid, develop pain-producing, uterus-stimulating activity when aspirated into glass syringes. By contrast, cardiac edema fluid (low in content of protein) develops no pain-producing activity and very little uterus-stimulating activity when brought into contact with glass. The finding that blood develops activity similar to that of exudates when withdrawn into a glass syringe is attributed to activation of the plasma. The similarity in behavior of inflammatory exudates and plasma is presumably due to the origin of these protein-rich exudates from plasma.

Activation by glass suggests some relation to blood clotting; however, it is interesting that pain-producing, uterus-stimulating activity develops before clotting occurs.[16] When blood or plasma is kept in contact with siliconed surface or in polyethylene vessels, both clotting and development of PPS are greatly delayed. On the other hand, anticoagulants do not inhibit the formation of PPS. It seems likely that contact with a glass surface might activate the precursor of plasmin, plasminogen, particularly since Rapaport and associates[84] have shown that several blood-clotting enzymes are activated in this way. Lewis[17] has recently shown that antiplasmin as well as soya-bean trypsin inhibitor will inhibit the glass activation of the formation of PPS. Characterization studies with glass-activated kinin (PPS) have been unable to distinguish this material from bradykinin.[14] Schachter[18] has shown that plasma diluted with physiologic saline develops smooth-muscle stimulating activity due to a substance similar to bradykinin and kallidin. However, Lewis[17] has presented data which argue against the activation of plasminogen to plasmin as the explanation for the dilution phenomenon. He reports that after dilution of plasma in siliconized vessels, smooth-muscle stimulating activity could be found, and that, furthermore, antiplasmin did not inhibit, whereas soya-bean trypsin inhibitor completely inhibited, the development of activity. It has also been shown that plasma treated with chloroform develops proteolytic activity[85] and exhibits smooth-muscle stimulating activity. Antiplasmin added to the plasma before it is treated with chloroform completely inhibits the formation of smooth-muscle stimulating activity.

Plasmin or fibrinolysin is a proteolytic enzyme which is found in blood and is normally present as an inactive precursor called *plasminogen*.[86] It has been discovered that extracts of many tissues are capable of activating plasminogen to the active proteolytic enzyme.[86] Evidence has been presented from a number of different sources[16-18,85] that a smooth-muscle stimulating substance can be formed by the reaction of plasmin with plasma globulins. Thus, injured tissues would allow passage of plasminogen activators, resulting ultimately in the formation of vasodilator plasma kinins which could then take part in the tissue reactions. Lewis[17] has made a rather extensive study of the material produced by the reaction of plasmin with plasma protein. Qualitatively as well as quantitatively, plasma kinin could not be distinguished from bradykinin on four different test systems. More recently, Back[87] has shown, in dogs, the formation of a vasodilator substance (plasma kinin) after injection of a plasmin preparation.

Recently, Ronwin[88] has carried out a series of studies concerning the active center of plasmin. Plots of the variation of pK_m and log V max. with pH for plasmin indicated that the active center of this enzyme is functionally identical to that of trypsin. Thus, it is not too surprising that plasmin and trypsin are capable of forming similar polypeptides if the substrate used is common to both of the enzymes. However, plasmin differs from kallikrein, another enzyme in blood,[6] in that the former is thermostable and resistant to acid.[17]

The proteolytic enzymes discussed up to now have all been animal in origin. A few years ago, Prado and associates[22] reported studies on a bacterial protease from *Clostridium histolyticum* which could react with plasma globulin to form a smooth-muscle stimulating, vasodilator material which could not be distinguished from bradykinin.

D. URINARY KININS

Urinary kinins can be defined as pharmacologically active polypeptides which bear a close relationship in physical and biological properties to the plasma kinins. The presence of vasodilator substances in urine have been reported by a number of investigators.[12,89-91] Werle and Erdos[12] were the first to systematically study the actions and properties of the urinary depressor substance. They characterized the effect of proteolytic enzymes upon this substance and named it *substance Z*. Gaddum had observed that diluted urine contracts the superfused rat uterus and suggested that the active substance may be a polypeptide. This was studied by Gomez,[13] who showed that the active substance was indeed a polypeptide, and that its properties were similar to those of bradykinin and substance Z. This work was extended by Walaszek,[15] who prepared a stable dry standard and was able to effect an appreciable purification by means of chromatography on alumina and paper pulp columns. By paper chromatography he was able to demonstrate two active polypeptides, which were provisionally named *substance* Z_1 and *substance* Z_2, using the notation of Werle and Erdos.[12] The conclusion reached was that this urinary substance was bradykinin, since bradykinin also could be separated into two components, and furthermore, parallel assay showed the biological properties to be similar. Jensen[92] described a new method for the isolation of substance Z by means of an ion-exchange column. He confirmed the results of Walaszek[15] by also isolating two active components from the urinary kinin. Gaddum and Horton[14] were unable to confirm the reports of Walaszek[15] and Jensen[92] that two substances were present. They introduced the use of rat duodenum for the biological assay of this material and concluded that substance Z was very closely related to bradykinin, kallidin, and plasma kinin.

It is of interest that Van Arman[50] presented evidence that bradykinin can be separated into two active components by paper chromatography. This would confirm the results of Walaszek,[15] who also showed two active components in bradykinin. Furthermore, Van Arman was able to show two components in kallidin: one was identical to that found in bradykinin but the other was different from the second component of bradykinin. It may be that the slight discrepancies

on parallel assays which were reported by Gaddum and Horton[14] between substance Z, bradykinin, kallidin, and glass-activated kinin may be due to the fact that all of them possess at least one component which is identical. At least in the case of kallidin, bradykinin, and substance Z there seems to be a second component which is either different or present in different ratios and tends to cause slight discrepancies in parallel assays.

Horton[71] reported the excretion of urinary kinin (substance Z) in human subjects. He found that the excretion was fairly constant and was not affected by rate of formation of urine, urinary pH, or time of day. There was no increase during sweating or salivation.

A polypeptide in dog urine was studied by Beraldo[7] and provisionally name *substance U.* Its properties were similar to those of kallidin, and undoubtedly it belongs to the group of urinary kinins represented by substance Z.

E. WASP KININ

In 1954, Jacques and Schachter[93] reported that the venom of the common wasp (*Vespa vulgaris*) contains high concentrations of histamine, 5-hydroxytryptamine, and a highly potent material which produces a characteristic delayed, slow contraction of the isolated guinea-pig ileum. Chemical and pharmacologic studies on this latter material in wasp venom have been carried out by Schachter and Thain.[20] Their results demonstrate that this substance, designated as ***wasp kinin***, or simply ***kinin***, is a dialyzable polypeptide which causes a contraction of the isolated rabbit jejunum, guinea-pig ileum, and rat uterus, and is a vasodepressor in the rabbit, cat, and dog.[20,21] Kinin also induced moderate pain when applied to a blister base on human skin, with results similar to the pain-producing substance described above.[21] The ability of kinin to increase capillary permeability to circulating dye was found to be one of its most striking pharmacologic properties. Experiments carried out by Holdstock and associates[21] have confirmed previous observations which indicate the pharmacologic similarity of kinin, kallidin, and bradykinin; however, kinin could not be distinguished from these other two polypeptides by paper chromatography and by differential sensitivity to inactivation by trypsin. Since the rat duodenum has been shown to relax in the presence of bradykinin, it would be of interest to know the actions of wasp kinin on this test preparation. There is no evidence to show that the occasional severe generalized reactions of human beings to wasp sting is due to the content of kinin in the venom.

F. COLOSTROKININ

Substances capable of stimulating smooth muscle may be produced by incubation of bovine colostrum with urinary kallikrein or calf saliva.[23,94] These substances have been called *urine* and *saliva colostrokinin* by Werle.[94] Chemical and pharmacologic studies of the colostrokinins by Guth[23] have indicated that urine colostrokinin is more similar to plasma kinin than is saliva colostrokinin. Further work must certainly be carried out before the identity of the colostrokinins is established, but present work would indicate that they are different from sub-

stance P, angiotensin, acetylcholine, histamine, and 5-hydroxytryptamine. It is highly interesting that as bovine colostrum becomes milk, a period requiring 3 to 4 days, the protein substrate diminishes in concentration, and this diminution coincides in the calf with the time at which the permeability of the gut to proteins is diminished.[23]

G. SUBSTANCE P

Substance P, a polypeptide which was first described by Euler and Gaddum,[95] occurs naturally in extracts of brain tissue and gastrointestinal tissue. It produces a potent stimulation of smooth muscle, and on the circulation it produces a vasodilatation. It has no effect on cardiac muscle. It has been conclusively shown that the agent in the tissue extracts which is responsible for the stimulating activity on smooth muscle is also responsible for the active vasodilating effect.[96] By various chemical and pharmacologic techniques it was established that substance P was not identical with any other known autopharmacologic substance.[97] Pernow,[42] in a scholarly publication, was able to effectively purify substance P from an extract containing 3 units per milligram to one with a potency of 3,000 units per milligram. Upon paper chromatography the smooth-muscle stimulating activity and vasoactive activity was found to have an Rf of 0.37.

The most sensitive preparations of smooth muscle which respond to substance P are the isolated guinea-pig ileum, rabbit jejunum, and rectal cecum of the hen. The effects of substance P are not blocked by atropine or antihistaminics, nor by ganglionic blocking agents. It was concluded, therefore, that substance P owes its stimulating effect on smooth muscle to a direct action on the fibers of the smooth muscle.[42] The depressor effect seen when substance P is injected intravenously is due to a peripheral vasodilatation. Vasodilatation can be observed on the blood pressure of the rat, cat, dog, and rabbit.

The distribution of substance P presents many interesting facets. In the digestive tract, substance P can be found in highest concentration in segments which have the most pronounced motility. There is a close correlation between the content of substance P, the degree of peristaltic activity, and the occurrence of ganglion cells in the intestinal wall.[98] In the central nervous system, the gray matter contains more substance P than does the white matter. The highest values are obtained from the hypothalamus, caudate nucleus, area postrema, nuclei cueneatus, and gracilis, and in the gray matter of the medulla spinalis.[42,99] Distribution of substance P in the central nervous system roughly parallels that of norepinephrine and serotonin. There is no information available in regard to the amino-acid composition of substance P. We are also totally ignorant of the biosynthesis of this polypeptide, but we are aware of the means by which its pharmacologic activity can be terminated. An enzyme has been described which can inactivate substance P,[100] but whether this is a specific enzyme or just a general proteolytic enzyme is not known at this time.

The physiologic role of substance P is not certain, but it seems definitely to be important in the proper functioning of the central nervous system. It was originally believed that substance P was the mediator for gastrointestinal motility.

It is more likely that the substance responsible for this is darmstoff.[101] A number of workers have put forward the view that substance P is a chemical mediator of the central nervous system.[99,102-104] The basis for postulating a neurohumoral role for substance P has been mainly its distribution in the central nervous system. To this end the idea is advanced that substance P is concerned with noncholinergic transmission. However, as was mentioned previously, the distribution of substance P in the central nervous system parallels that of serotonin, norepinephrine, and acetylcholine. This is not the type of distribution that one could accept for a noncholinergic transmitter.[105] The content of substance P in the dorsal columns of the cord is high. Its presence in this noncholinergic tract indicates that it may be a mediator of synaptic transmission for the sensory neurones.

It has been reported[106] that lysergic acid diethylamide (LSD), the hallucinogen, can potentiate the action of substance P on the isolated guinea-pig ileum. LSD was also capable of inhibiting the enzyme in brain tissue that inactivates substance P. In a recent report by Smith and Walaszek,[107] the potentiating effect of LSD on the action of substance P has been confirmed, but it was shown that other polypeptides (bradykinin and substance A) were also potentiated by LSD. Furthermore, upon prolonged exposure of the isolated guinea-pig ileum to LSD, an antagonism was observed. The afore-mentioned investigators were unable to inhibit the enzyme of inactivation in intestinal tissue nor were they able to demonstrate a change in the content of substance P in the hypothalamus and caudate nucleus of rabbits pretreated with LSD. The conclusion reached was that the potentiating effect of LSD is unspecific and not related to the hallucinogens. However, LSD and other hallucinogens (harmine, ibogaine, and adrenochrome) were able to antagonize the actions of substance P.

The recent work of Stern and his co-workers[108] deserves our attention. These workers were able to demonstrate that substance P is synergistic with meprobamate and mephenesin in inhibiting polysynaptic neurons. Zetler[109] reported that substance P had a sedative effect, and that it antagonized strychnine convulsions and harmine tremors. Stern and co-workers[110] were able to show that substance P had tranquilizing properties. Wild hares injected with substance P became tame rabbits, and the concentration of substance P in their brains became elevated. These workers suggest that substance P may play the role of a physiologic tranquilizer. In a recent report, Stern[111] was able to demonstrate that reserpine increases the content of substance P in the brain. It may very well be that the tranquilizing properties of reserpine are more closely related to the content of substance P in the brain rather than to the ability of this drug to release the biogenic amines serotonin and norepinephrine.

This finding suggests that perhaps substance P may be very important in mental disorders. Walaszek[112] was able to demonstrate that rabbits pretreated with schizophrenic serum presented a lowered level of substance P in the brain when compared to rabbits pretreated with normal serum.

SUMMARY

The physiologic and the pharmacologic properties of a group of closely related vasodepressor polypeptides have been described. Bradykinin has been

used as the model polypeptide for our discussions, with the other vasodepressor polypeptides described from the standpoint of their similarities and differences. The other polypeptides include kallidin, plasma kinin, substance Z, clostridin, colostrokinin, wasp kinin, and substance P. All of these pharmacologically active substances, except wasp kinin and substance P, may be produced by the action of a proteolytic or an esterolytic enzyme upon a substrate found in the α^2-globulin fraction of plasma protein. It is not known at the present time whether the other polypeptides which cannot be distinguished pharmacologically from bradykinin have the same chemical constitution. They all possess the property of producing a depressor effect when injected intravenously, and will produce a contraction on the isolated uterus and intestine. Their pharmacologic effect is destroyed by incubation with chymotrypsin, but not by trypsin or pepsin, except for substance P, which is destroyed by all three enzymes. Evidence has been presented that these active substances may be involved in functional vasodilatation in secretory organs and skin, and in increasing the flow of blood in skeletal muscle. It has been found that these polypeptides may be involved in the neurohumoral features of the axon reflex. The depressor-polypeptide-forming mechansim may be involved in a number of pathologic phenomena, such as active disease of the central nervous system, vascular headache of migraine type, anaphylactic and peptone shock and other traumatic episodes. Substance P appears to be important in the proper functioning of the central nervous system, and may serve as a chemical mediator in this system.

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Annotations

The Role of Histamine

Histamine has long been known to be a normal constituent of the body,[1,2,3] and it is distributed widely throughout the tissues. It is a potent vasodilator substance, and many attempts have been made to incriminate it as the mediator of a number of physiologic vasodilator phenomena. Lewis[4,5] postulated that a histamine-like substance was responsible for the "flare" of tissue injury, for cold vasodilatation, and for reactive hyperemia. Barsoum and Smirk[6] and Anrep and associates[7] found a rise in the level of plasma histamine in the effluent blood after circulatory arrest and venous congestion and during postexercise hyperemia. Staub[8] attributed the vasodilator effect of adrenaline to the release of histamine.

More recent studies in man using both assay of plasma histamine and the application of antihistamines have failed, however, to provide evidence for the involvement of histamine in adrenaline vasodilatation,[9] cold vasodilatation,[10,11] reactive hyperemia,[12] or exercise hyperemia.[11] Thus, by 1955, apart from the anaphylactic response[13] and its possible involvement in gastric secretion,[14] histamine seemed to be "devoid of physiological significance."[13]

In a recent report by Kahlson,[15] however, a new approach to the problem is described which places the emphasis on the rate of formation, rapidity of turnover, and rate of usage of histamine rather than on its content in tissue or fluid. Formation of histamine was followed in rats by feeding 14_C-labelled histidine and measuring the urinary 14_C-histamine. Formation increased during pregnancy, and fell abruptly shortly before term. The source was shown to be the fetal liver, where the turnover was rapid, although the content was low and loosely bound. Turnover of histamine was also found to be greatly increased during regeneration of liver after excision, whereas the healing of wounds was enhanced by mobilization of histamine by 48/80 and retarded by histamine-deficiency brought about by semicarbazide, an inhibitor of histidine decarboxylase. Reduction in the formation of histamine by semicarbazide also resulted in inhibition of fetal growth. It is concluded that histamine is probably connected in some way with the metabolic processes of development, growth, and repair. The author is careful to point out that the situation is a complex one and that it is not yet possible to say whether the observed changes in the formation of histamine are essential to the events studied or are parallel but not causative events. However, the observations open up a new field of enquiry, and an understanding of the role of histamine in normal physiologic processes may not be so far distant as it seemed in 1955.

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Atherosclerosis—What Diet?

Authorities in general agree that heredity, maleness, hypertension, overweight, and excessive dietary intake of fat from animal sources may be factors that predispose individuals to the development of atherosclerosis. The list might be amplified to include smoking, overeating in general, and lack of physical activity, and there may be factors unknown to us at the present time. The exact role of the dietary intake of fat is debatable. Although it has been established that restriction and alteration of dietary fats will lower serum cholesterol in man, there is as yet no positive proof that this accomplishment will reverse atherosclerosis or prevent thrombosis or infarction. The literature dealing with all phases of this controversy is abundant.[1,2]

In spite of the fact that there is at present no general agreement among physicians on this subject, many believe that frequently the dietary intake of fat should be altered in an attempt to lower the level of blood lipids. They realize that this is an experimental approach, pending final evaluation of the lipid problem, which may be many years away. What diet is most likely to be successful in accomplishing this and be at the same time acceptable to the average patient? In general, the total intake of fat of animal origin should be limited to 25 to 30 grams daily, and the percentage proportion of all fats to total caloric intake should not exceed 40. This means the virtual elimination of dairy products, margarine, lard, hydrogenated shortenings, and egg yolks (skim milk and skim-milk cheese are exceptions). Red meat, lamb, veal, and pork, although permitted in moderation, should be carefully trimmed of fat; fowl, fish, and seafood may be liberally substituted for meat. It is now apparent that whereas a high dietary intake of saturated fats raises serum cholesterol, just the reverse effect results from intake of foods of vegetable origin containing poly-unsaturated fatty acids. Thus, a successful cholesterol-lowering diet should contain unsaturated fats, particularly those which contain linoleic acid. The proper proportion of animal to vegetable fats is approximately 1 to 3. Corn oil is an admirable source of vegetable fat, and may be used to prepare salad dressing, for frying, and for spreads to replace butter.[2,8,9]

How to put these basic dietary requirements together so that the patient will follow instructions is a real problem. A competent dietician is invaluable, but if one is not available, there are several particularly useful dietary guides that are readily available, such as, *Low Fat Cookery*,[3] *Eat Well and Stay Well*,[4] and a group of excellent sample menus.[5,6]

Every physician with experience in these matters has learned that patients are divided, roughly, into two groups: first, those whose levels of blood cholesterol fall readily in response to a low-fat diet, and secondly, those whose do not. Brown and Page[7] have clarified this experience

by describing three distinct types of hyperlipemia and pointing out that the patients who exhibit them react quite differently to a restriction of dietary fat. There are those with (1) hyperglyceridemia in whom the triglycerides are much higher than cholesterol; (2) hypercholesteremia (with normal triglycerides); and (3) a mixture of the two. In this latter group, all serum lipids are elevated but are in normal proportion to each other. The results of Brown and Page suggest that the physician, with knowledge of the type of serum lipid abnormality with which he deals, is in a position to prescribe dietary treatment with reasonable assurance of the outcome. Patients with type 1 show a fair response, those with type 3 show a good response, and those with type 2 show a poor response.

Boyer and co-workers[8] describe a relatively simple transition from a normal to a restricted diet by the use of a corn oil margarine containing 64.2 per cent of nonhydrogenated corn oil, in place of all solid fat, corn oil for all liquid fat, skim milk for whole milk, and sherbert for ice cream.

The American Heart Association has in preparation a booklet for a fat-controlled diet, with a carefully adjusted ratio of saturated to unsaturated fat. This booklet is planned for the use of physicians, and will be accompanied by material for the patient.

A word of caution is in order in regard to total calories in the diet. This important item may be easily overlooked in the concern for the individual components of the menu. It is generally agreed that a reduction in weight and the maintenance of the reduction are important parts of the therapeutic effort under consideration.

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Vasoconstrictor Innervation of Human Skeletal Muscle

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level as that found after block of the deep nerves to the muscles of the forearm[7]; within a week, however, it had returned to the preoperative level. A similar picture was seen in the calf, but the mechanism of the return of tone to sympathectomized vessels is not fully understood.[8]

Although the experiments of Barcroft and associates[5] demonstrated a vasoconstrictor innervation of muscle, there was no clear indication at that time of the part played by the fibers in the normal regulation of the circulation. They did not take part in the reflex responses to such stimuli as a deep breath, a pinch, application of ice to the skin, etc., which normally cause reflex vasoconstriction in the hand.[9] Although some experiments suggested that vasoconstrictor tone in muscle might be released in response to heating the body,[10,11] it was subsequently found that the vasodilatation in the forearm during heating of the body was confined to the skin.[12-16] It now seems that the "vasomotor centers" which control blood vessels in skin and muscle can function quite independently of one another.

The reflex effects on peripheral blood vessels of passively raising the legs of a recumbent subject have been studied in considerable detail.[17-19] Although this stimulus caused reflex vasodilatation in the forearm, there was no comparable change in the hand. Raising the legs caused an increase in the oxygen saturation of blood sampled from the veins of the forearm which drained muscle, whereas no change occurred in blood sampled from veins which drained skin. These findings suggested that the vessels in muscle rather than those in skin are responsible for the vasodilatation. The vasodilatation in muscle was mediated through sympathetic vasomotor fibers, since it was abolished by acute nerve block and by cervical sympathectomy. Release of vasoconstrictor tone rather than activity of vasodilator fibers seemed to be responsible for the changes in the flow of blood in muscle. In no case was the vasodilatation greater than could be accounted for by release of vasoconstrictor tone; the vasodilatation was not reduced by atropinizing the forearm, but was abolished by intra-arterial infusion of bretylium tosylate, a sympatholytic agent. It was concluded that alterations in vasoconstrictor tone in muscle were responsible for the changes in the flow of blood in the forearm, with change in posture.

Recently, a wide variety of stimuli have been found to cause reflex alterations in the flow of blood in the forearm which are thought to be due to alteration in vasoconstrictor tone in muscle. Raising the legs of a recumbent subject,[17] negative pressure breathing,[20] squatting,[21] and intrathoracic pressure transients[22,23] cause reflex vasodilatation. Tilting the subject into the vertical position,[24] positive pressure breathing,[20] the Valsalva maneuver,[23,25] exercise,[26] radial acceleration,[27] and hypercapnia[28] cause reflex vasoconstriction.

The precise location of the receptors concerned with reflex regulation of vasoconstrictor tone in muscle is not known, nor is the exact nature of the stimulus. It has been suggested that changes in arterial pulse pressure may be responsible for the observed changes: a fall in arterial pulse pressure may cause vasoconstriction, and an increase may cause vasodilatation.[21] Stimulation of the carotid sinus nerve in man has been found to cause a fall in the resistance to the flow of blood in the forearm.[29] During tilting from the horizontal to the feet-down position, pulse pressure is usually reduced and vasoconstriction in the forearm is the rule[24]; during squatting, pulse pressure is usually increased and is accompanied by vasodilatation.[21] However, many experimental findings cannot be explained by this hypothesis. It was not found possible to correlate the increase in the flow of blood in the forearm during leg raising with an increase in either arterial mean or pulse pressure.[18] In many cases a large increase in the flow of blood in the forearm occurred without any change, or even with a fall, in pulse or mean pressure. After the Valsalva maneuver there is an increase in pulse and mean pressure. Although this is associated with bradycardia, it is not accompanied by vasodilatation[23,25]; intense vasoconstriction is usually seen. During leg exercise, vasoconstrictor tone is greatly increased in the muscle of the forearm, even though there is a substantial rise in arterial mean and pulse pressure.[26] Raising or lowering the effective pressure at the carotid sinus by application of subatmospheric pressure to the neck,[30] or by manual compression of the carotid arteries,[31] respectively, produce the classic changes in arterial pressure and heart rate, yet they are not accompanied by important changes in the resistance to the flow of blood in the limbs. In view of these findings it is unlikely that responses to changes in arterial pressure can fully explain the alterations of vasoconstrictor tone in muscle.

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by describing three distinct types of hyperlipemia and pointing out that the patients who exhibit them react quite differently to a restriction of dietary fat. There are those with (1) hyperglyceridemia in whom the triglycerides are much higher than cholesterol; (2) hypercholesteremia (with normal triglycerides); and (3) a mixture of the two. In this latter group, all serum lipids are elevated but are in normal proportion to each other. The results of Brown and Page suggest that the physician, with knowledge of the type of serum lipid abnormality with which he deals, is in a position to prescribe dietary treatment with reasonable assurance of the outcome. Patients with type 1 show a fair response, those with type 3 show a good response, and those with type 2 show a poor response.

Boyer and co-workers[8] describe a relatively simple transition from a normal to a restricted diet by the use of a corn oil margarine containing 64.2 per cent of nonhydrogenated corn oil, in place of all solid fat, corn oil for all liquid fat, skim milk for whole milk, and sherbert for ice cream.

The American Heart Association has in preparation a booklet for a fat-controlled diet, with a carefully adjusted ratio of saturated to unsaturated fat. This booklet is planned for the use of physicians, and will be accompanied by material for the patient.

A word of caution is in order in regard to total calories in the diet. This important item may be easily overlooked in the concern for the individual components of the menu. It is generally agreed that a reduction in weight and the maintenance of the reduction are important parts of the therapeutic effort under consideration.

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The precise location of the receptors concerned with reflex regulation of vasoconstrictor tone in muscle is not known, nor is the exact nature of the stimulus. It has been suggested that changes in arterial pulse pressure may be responsible for the observed changes: a fall in arterial pulse pressure may cause vasoconstriction, and an increase may cause vasodilatation.[21] Stimulation of the carotid sinus nerve in man has been found to cause a fall in the resistance to the flow of blood in the forearm.[29] During tilting from the horizontal to the feet-down position, pulse pressure is usually reduced and vasoconstriction in the forearm is the rule[24]; during squatting, pulse pressure is usually increased and is accompanied by vasodilatation.[21] However, many experimental findings cannot be explained by this hypothesis. It was not found possible to correlate the increase in the flow of blood in the forearm during leg raising with an increase in either arterial mean or pulse pressure.[18] In many cases a large increase in the flow of blood in the forearm occurred without any change, or even with a fall, in pulse or mean pressure. After the Valsalva maneuver there is an increase in pulse and mean pressure. Although this is associated with bradycardia, it is not accompanied by vasodilatation[23,25]; intense vasoconstriction is usually seen. During leg exercise, vasoconstrictor tone is greatly increased in the muscle of the forearm, even though there is a substantial rise in arterial mean and pulse pressure.[26] Raising or lowering the effective pressure at the carotid sinus by application of subatmospheric pressure to the neck,[30] or by manual compression of the carotid arteries,[31] respectively, produce the classic changes in arterial pressure and heart rate, yet they are not accompanied by important changes in the resistance to the flow of blood in the limbs. In view of these findings it is unlikely that responses to changes in arterial pressure can fully explain the alterations of vasoconstrictor tone in muscle.

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which are known to cause reflex changes in muscle lead to redistribution of blood between the chest and the rest of the body. The vasodilatation in muscle during leg raising has been shown to depend on the return of blood from the legs to the chest.[18] Many receptors have been described in the walls of low-pressure vascular components in the chest, especially the right and left atria and the intrapericardial portions of the superior and inferior venae cavae.[32,33] Afferent vagal impulses have also been observed which are related to the atrial pressure and volume cycle,[33,34] and to the pressure cycle in the pulmonary artery.[35] Although the effect of these impulses on cardiovascular activity remains obscure, it may be that they play a part in the reflex regulation of peripheral blood flow. However, the interrelationships of the various receptor mechanisms which are concerned in the reflex regulation of the circulation are complex and difficult to analyze with precision. In man, general anesthesia has been found to depress or abolish the reflex changes in vasoconstrictor tone in muscle during postural change,[36] so that the value of experiments designed to study these problems in anesthetized animals may be limited. There are still great technical difficulties in making simultaneous measurements of pressures and volumes in the various compartments in the central vascular system in conscious man, but little progress in locating the receptors is likely until such measurements become possible.

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The Repair of Atrial Septal Defects

A variety of techniques has been utilized during the last 10 years for the closure of interatrial septal defects, but, with the passage of time, only three procedures are now in common use, viz., the atrial well, hypothermia, and cardiopulmonary bypass.

The first of these is the only one of the "blind" techniques that has stood the test of time, and several large series have been reported with low mortality rates and satisfactory results.

Hypothermia has likewise been employed extensively, and several large series reported in the literature would indicate that it is also an acceptable technique, although, as with the atrial well, the method is only suitable for the septum secundum and sinus venosus type of defects.

It would seem that the increasing safety of bypass operation makes this the method of choice for dealing with the majority of atrial septal defects. Closure under direct vision without the limitations in time imposed by the hypothermic technique makes the whole procedure controlled and deliberate. It is, of course, essential that the bypass procedure employed should not, of itself, cause any significant mortality; and it should also be remembered that its use implies greater demands on the ancillary services of the hospital and the blood bank. Nevertheless, it is the only technique that allows septum primum defects to be closed with certainty and safety, and the time available enables any unforeseen difficulties to be more efficiently and safely overcome than with any other technique.

Although the specialized diagnostic facilities now available usually allow an accurate diagnosis of the type of defect and situation of the pulmonary veins, it occasionally happens that the operative findings are not in accordance with the preoperative diagnosis. When the bypass technique is employed, this is not of serious significance, since all types of atrial septal defects are amenable to closure with its use. Now that uncomplicated atrial septal defects can be closed with little risk, it would appear justifiable to recommend their routine closure except when the defect is so small that it is unlikely to materially reduce the patient's normal expectation of life. There would appear to be every reason for recommending operation in childhood, since the technical difficulties are very much less and there is less opportunity for major complications to develop. If bypass is to be employed, operation should, in general, be recommended between the ages of 4 and 8 years. There is every reason to believe that, as with the patent ductus arteriosus, once the defect has been closed, the heart will return to normal and a full expectancy of life will be restored to the patient.

Douglas H. Cohen, M.B., M.S., F.R.A.C.S.
Camperdown, Australia

Announcement

Physicians and surgeons from three nations will participate in an International Clinical Postgraduate Program to be offered by University of California Extension in January, 1961.

The second annual program, sponsored jointly by the School of Medicine of U.C.L.A., Universidad Nacional Autonoma de Mexico, University of Guadalajara School of Medicine, and Escuela Nacional de Medicina, Mexico, D.F., is an illustration of international cooperation in the field of medicine. It is designed to give participating doctors an unusual opportunity to avail themselves of different types of case material in this section of the American continent. The program, which will convene in Mexico City, continue in Acapulco, and close in Guadalajara, will be as follows:

In Mexico City: Monday, January 9—Gastroenterology and Internal Medicine will be discussed by Dr. Raul Fournier Villada, Dean of the School of Medicine at University City in Mexico City, and Dr. Sherman M. Mellinkoff and Dr. Bernard Sepulveda. January 10—Cardiology, by Dr. Ignacio Châvez, Dr. Demetrio Sodi-Pallares, and Dr. Forrest H. Adams, at the National Institute of Cardiology. January 11—Pediatrics, by Dr. Forrest H. Adams and Dr. Lazaro Benvides, at the Children's Hospital. January 12—Dermatology and Mycology, by Dr. Antonio G. Gonzales Ochoa and Dr. Thomas H. Sternberg, at the Institute of Tropical Diseases. January 13—General Surgery, by Dr. Guillarmo Alamilla, Dr. Harvey M. Lippman, and Dr. Angel Matute, at the Spanish Hospital.

In Acapulco: January 15—Obstetrics and Gynecology, by Dr. J. George Moore and Dr. Bernardo Castro Villagrana. January 17—Traumatic Surgery, by Dr. Franklin L. Ashley, Dr. Aurelio Perez Teuffer, and Dr. Mario Gonzales Ulloa.

In Guadalajara: Topics for study through January 20 will be announced.

Requests for additional information or applications concerning the course should be made to: Thomas H. Sternberg, M.D., Assistant Dean for Postgraduate Medical Education, University of California Medical Center, Los Angeles 24, Calif. (Phone GRanite 8-9711 or BRadshaw 2-8911, Station 7114).

AMERICAN HEART JOURNAL

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Editorial Communications

Original Communications.—Manuscripts for publication, letters, and all other communications relating to the editorial management of the Journal should be sent to the Editor, Dr. George E. Burch, 1430 Tulane Avenue, New Orleans 12, Louisiana. Articles are accepted for publication with the understanding that they are contributed solely to the American Heart Journal.
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safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

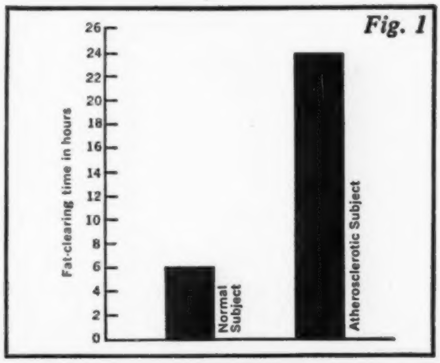

Fig. 1

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2,* the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

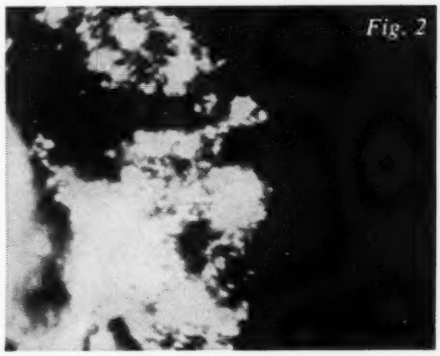
Fig. 2

In *figure #3,* the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

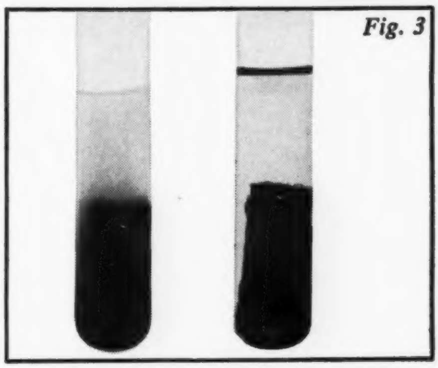
Fig. 3

'Clarin', which is heparin in the form of a *sublingual tablet,* has been demonstrated to clear lipemic serum.[2,6,7] Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarin'.[8]

'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

References: **1.** Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. **2.** Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. *7*:225 (Apr.) 1959. **3.** Stutman, L. J., and George, M.: Clin. Res. *7*:225 (Apr.) 1959. **4.** Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. **5.** Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. **6.** Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. **7.** Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. **8.** Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: 'Clarin' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

Clarin*

(sublingual heparin potassium, Leeming)

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc.
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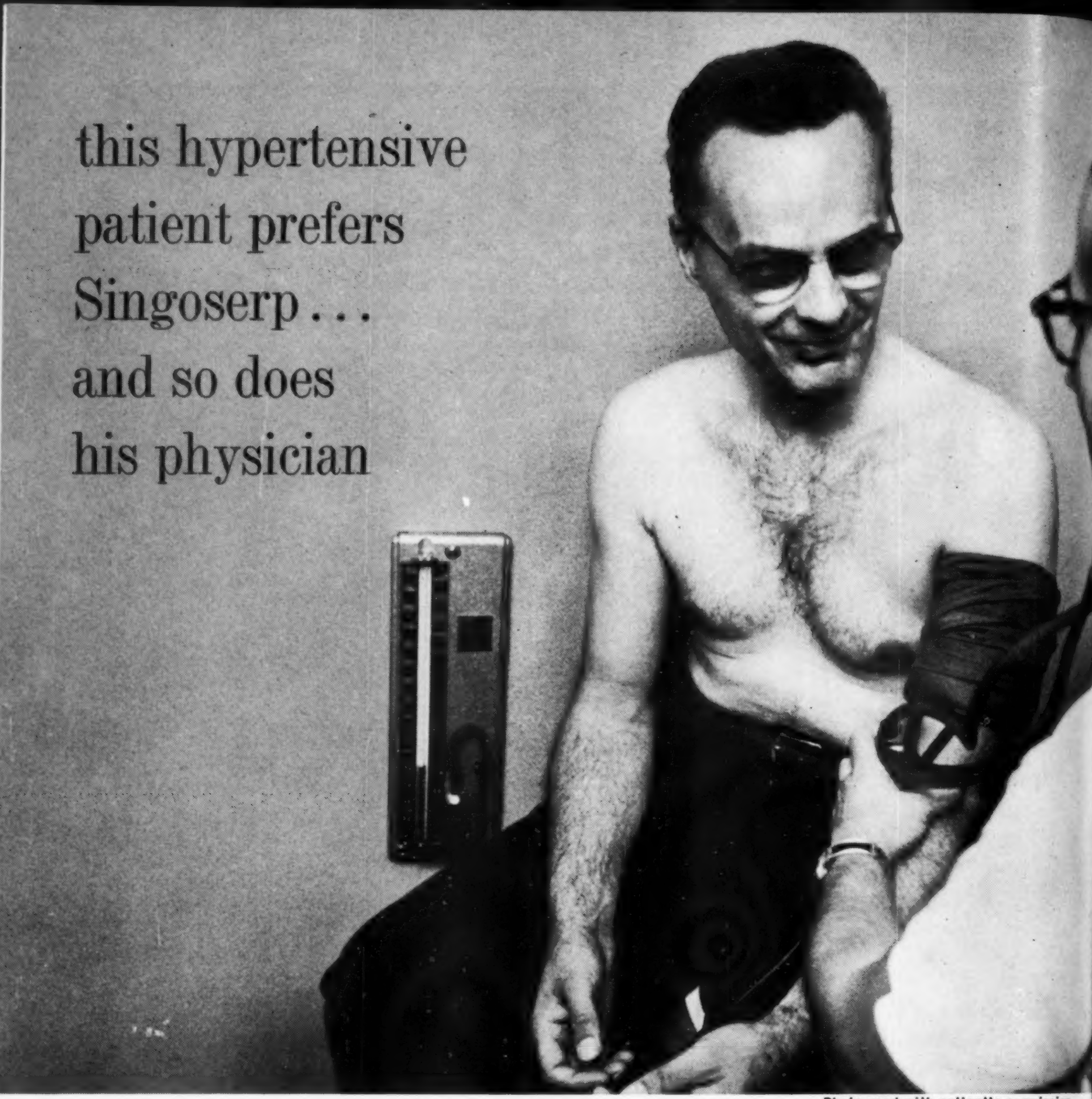

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Patient's comment: "The other drug [whole root rauwolfia] made me feel lazy. I just didn't feel in the mood to make my calls. My nose used to get stuffed up, too. This new pill [Singoserp] doesn't give me any trouble at all."

Clinician's report: J. M., a salesman, had a 16-year history of hypertension. Blood pressure at first examination was 190/100 mm. Hg. Whole root rauwolfia lowered pressure to 140/80—but side effects were intolerable. Singoserp 0.5 mg. daily, further reduced pressure to 130/80 and eliminated all drug symptoms.

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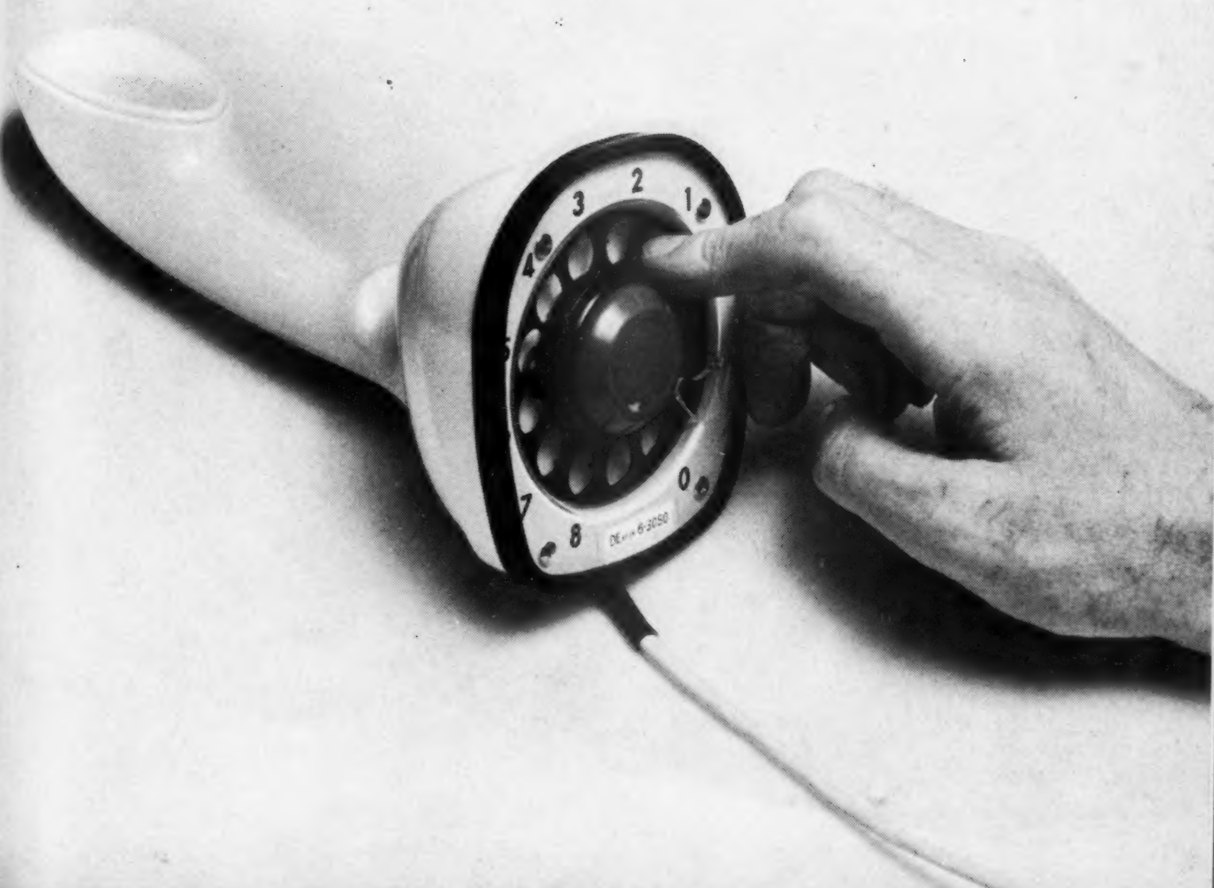

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an improved way to treat edema and hypertension

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If you've found the thiazide diuretics helpful, you'll particularly appreciate Enduron. It provides the familiar benefits of oral thiazide therapy, but in a new and (we feel) more practical manner. ■ Dosage, for example, is engineered for the most practical schedule of all: "Once a day, every day." Easy to remember, easy to stick to. ■ More important, *duration* of action of this single daily dose is over 24 full hours. This means your first dose is still producing good diuresis or hypotensive action right up to the time when the next day's dose takes effect. ■ A single dose of 10 mg. produces a peak natruretic effect. By this we mean that the maximum possible effect occurs with 10 mg., and greater doses do not produce greater natruresis. However, most patients require just 5 mg. daily for satisfactory response. Some can be maintained on as little as 2½ mg. Such small doses afford a very safe therapeutic ratio. ■ If you're concerned about potassium, too, you'll like Enduron. It produces the least potassium excretion of any available thiazide. Depletion seldom becomes a factor in your therapy.

See next page for more details . . .

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logical culmination to thiazide therapy

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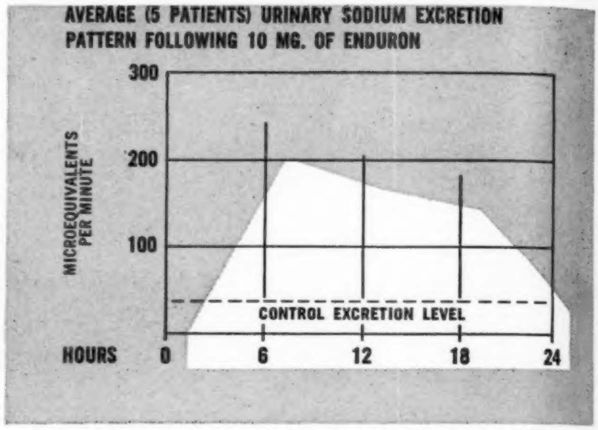

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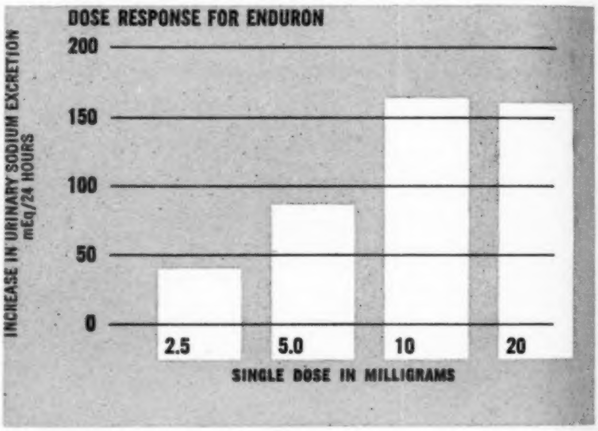

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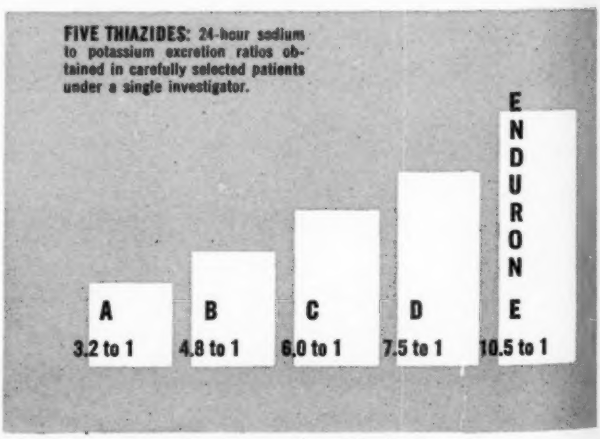

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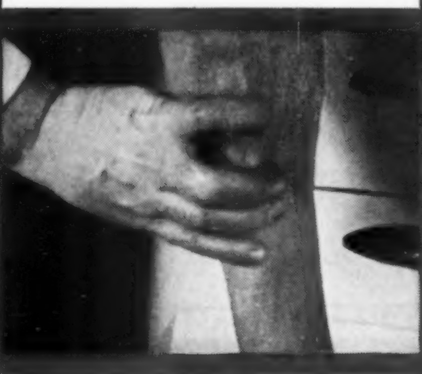
patient with congestive heart failure; ascites and 4+ edema to the knee



with Esidrix, 12⅜ pounds lost in 13 days; basilar râles and ascites no longer present; pitting edema cleared

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MER/29 *reduces total body cholesterol in 8 out of 10 —and these are the patients most likely to benefit*

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MER/29 reduces both serum and tissue cholesterol, irrespective of diet.[1] In 463 patients, the mean cholesterol was reduced from 324 mg.% to 253 mg.% — an average decrease of 71 mg.%.[1-6]

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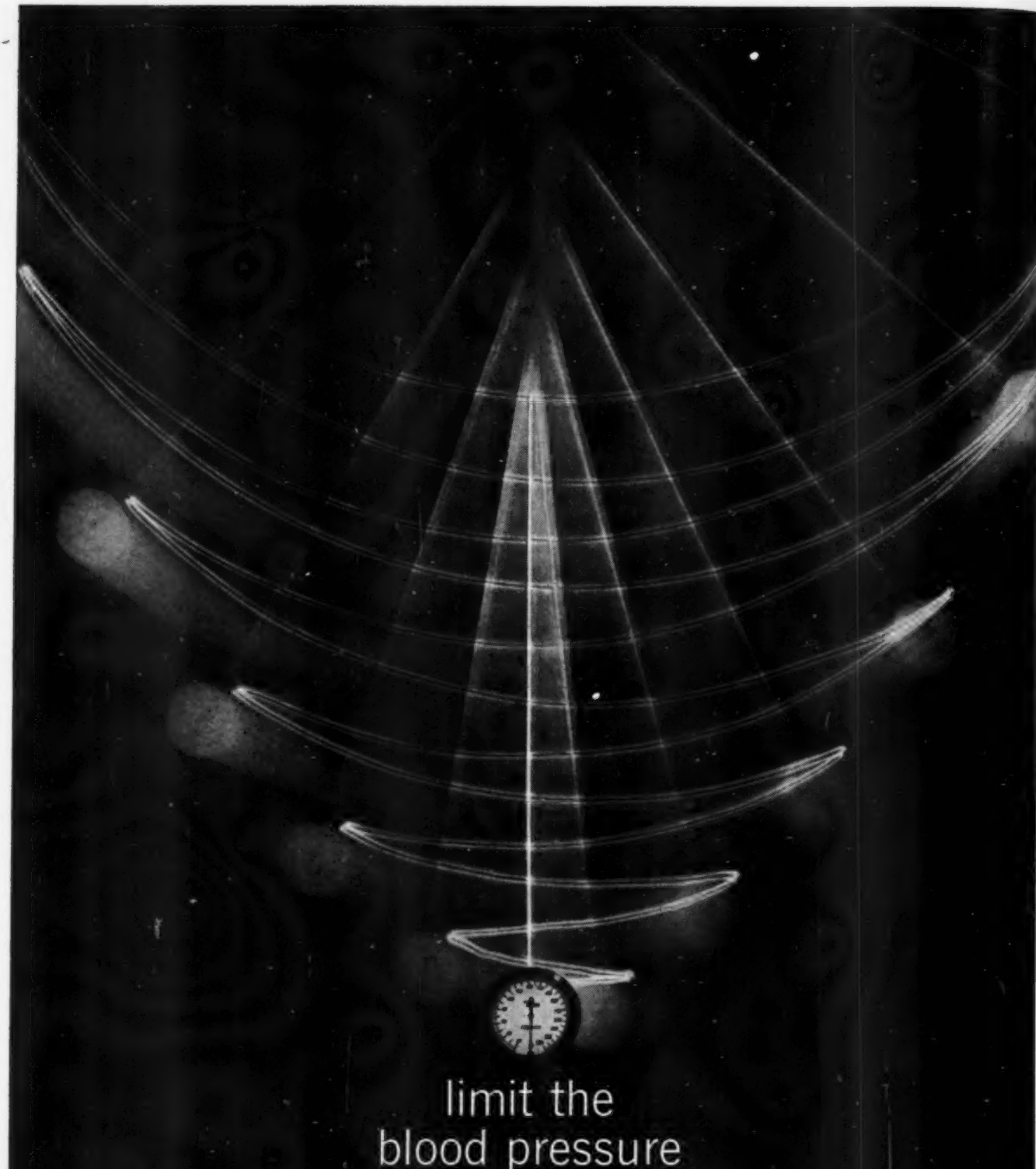
REFERENCES: **1.** Gifford, R. W., Jr., *In* Hypertension, ed. by J. H. Moyer, Saunders, Philadelphia, 1959, p. 561. **2.** Moyer, J. H.: *Ibid.* p. 299. **3.** Brodie, B. B.: *In* Hypertension, Vol. VII, Proceedings Council for High Blood Pressure Research, Am. Heart Assn., ed. by F. R. Skelton, 1959, p. 82. **4.** Wilkins, R. W.: Ann. Int. Med. 50:1, 1959. **5.** Freis, E. D.: *In* Hypertension, ed. by Moyer, *op. cit.*, p. 123. **6.** Ford, R. V., and Nickell, J.: Ant. Med. & Clin. Ther. 6:461, 1959. **7.** Fuchs, M., and Mallin, S. R.: Int. Red. Med. 172:438, 1959.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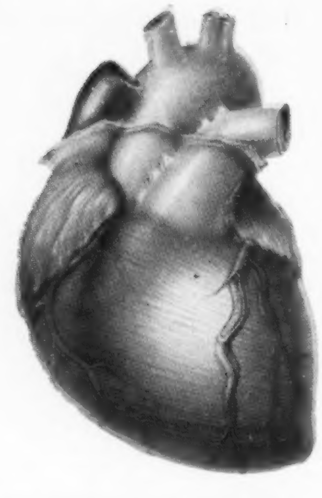
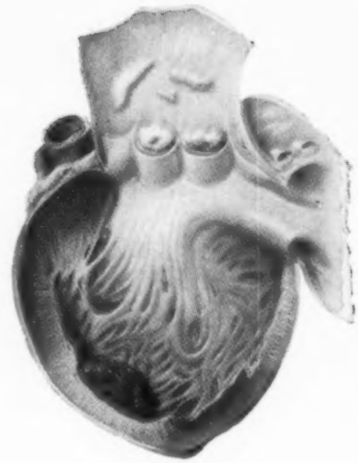
swing



IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

... the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



AFTER MYOCARDIAL INFARCTION

... it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

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Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

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Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

REFERENCES

1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J. E. F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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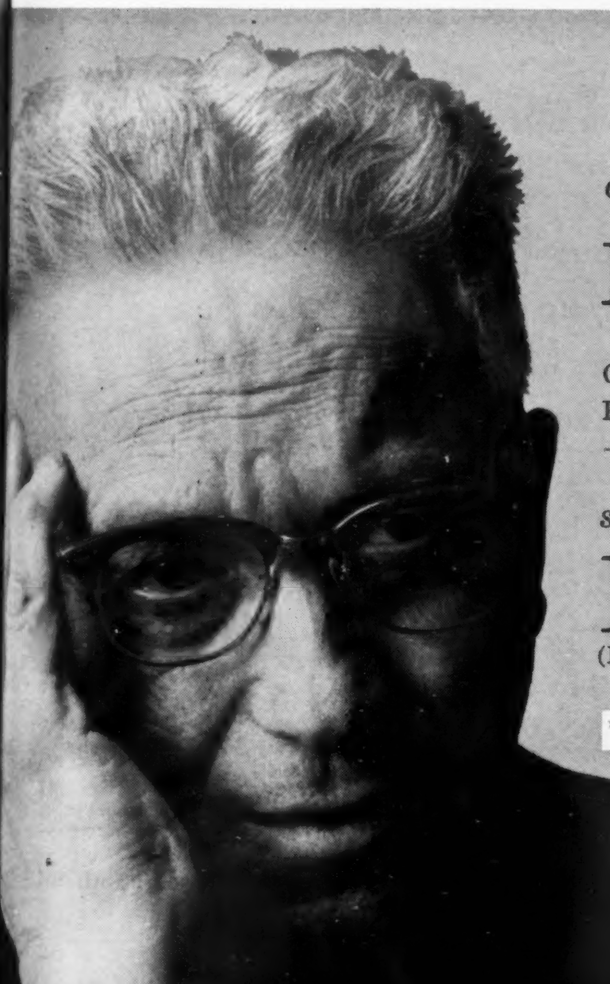

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DEPRESSION?

Of 403 Hypertensive and Mixed Anxiety Patients Treated With Harmonyl, only 6 —1.5%—Reported Depression.

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(Deserpidine, Abbott)

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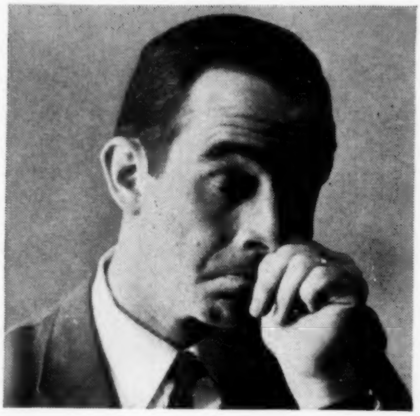

Nasal Congestion in Drug Treatment of Hypertension

Of 446 Hypertensive and Mixed Anxiety Patients Treated With Harmonyl®, only 12—2.7%—Reported Nasal Congestion

Presented are notes from four clinical studies. Harmonyl was used as sole agent of therapy by 446 mixed hypertensives, and patients with mild functional/psychiatric disorders. Only 12 reported nasal congestion concurrent with therapy—an incidence of 2.7%.

Study #1. Two hundred and eighty-three patients treated in private practice, at hospital outpatient clinics, and in office psychiatric practice. Average initial dosage of Harmonyl was 0.1 mg. to 0.25 mg. three or four times daily. No patient received more than 6 mg. daily. Two reports of nasal congestion (mild).

Study #2. Eighty patients with benign essential hypertension were studied via "double-blind" method. Mean daily dosage of Harmonyl was 0.25 mg., with a minimum dosage of 0.1 mg. and a maximum of 0.5 mg. daily. Eight reports of nasal congestion.

Study #3. Forty patients with hypertension and anxiety neurosis . . . from mild to moderately severe. Half of the group had received other antihypertensive agents at one time or another; these were discontinued before and throughout the study. Usual dosage of Harmonyl was 0.1 mg. three times daily after meals. Sometimes an additional dose was taken at bedtime. One report of nasal congestion (mild).

Study #4. Forty-three patients with tension and anxiety problems typical of those seen in general practice. Studied by "double-blind" method. Dosage was 0.25 mg. Harmonyl three times daily. One report of nasal congestion.

These and other investigators have noted that the side-effects seen with Harmonyl therapy are almost always mild and generally will not interfere with the patient's work or living habits.

1. Billow, B.W. et al., The Use of a New Rauwolfia Derivative, Deserpidine, in Mild Functional Disturbances and Office Psychiatry, N.Y. J. Med., 59:1789, May, 1959.
2. Winsor, T., Comparative Effects of Various Rauwolfia Alkaloids in Hypertension, Diseases of the Chest, 35:415, April, 1959.
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switch your working hypertensives to

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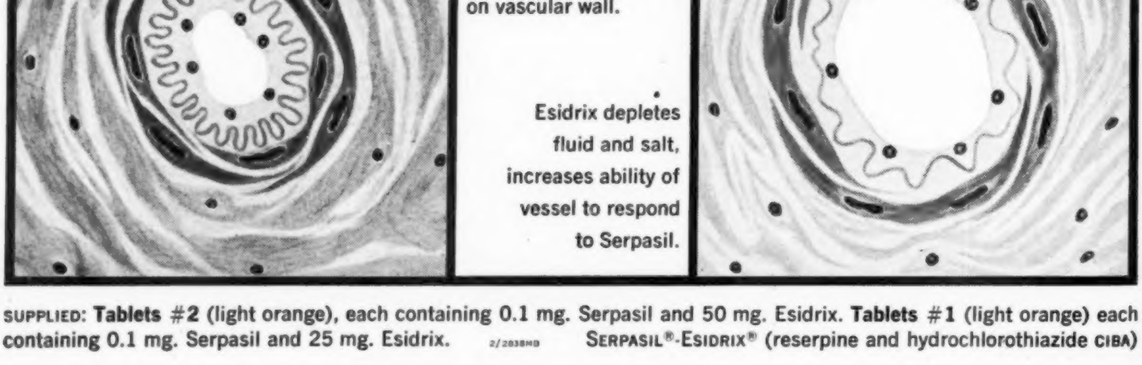

SUPPLIED: **Tablets #2** (light orange), each containing 0.1 mg. Serpasil and 50 mg. Esidrix. **Tablets #1** (light orange) each containing 0.1 mg. Serpasil and 25 mg. Esidrix. SERPASIL®-ESIDRIX® (reserpine and hydrochlorothiazide CIBA)

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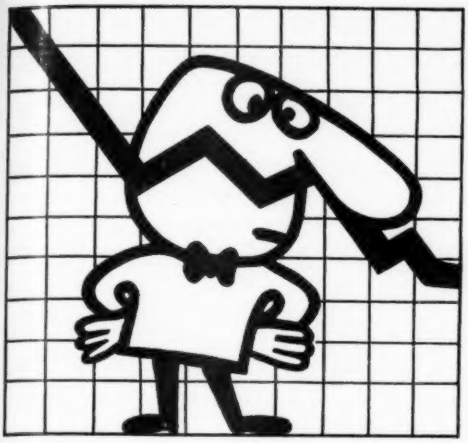

A U. S. Senator recently said, "In investigating the pharmaceutical industry, we are investigating and inquiring into an industry that has won and which deserves public approval and confidence... It has been my judgment that the hearings to which I have referred, so far have been prejudiced and distorted." To paraphrase a political saying...

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In relation to "real income," drug prices have actually declined in recent years. At prevailing wages in 1929, it took 91 minutes of working time to pay for the average prescription. Only 86 minutes of labor paid for the average prescription in 1958. As one economist put it, "If the retail prices of drugs had risen as much as the consumer price index since 1939, it would cost the consumer at least an additional one billion dollars to buy the drug preparations now consumed." He goes on to compare the $19.02 per capita drug expenditure in 1958 with the $37.19 spent on tobacco products and $53.72 for alcoholic beverages. • When your patients inquire about the cost of medication, perhaps these facts will be helpful in explaining that today's prescription, averaging about $3.00, is a relatively modest investment in better health and a longer, more productive life.

This message is brought to you in behalf of the producers of prescription drugs. For additional information, please write Pharmaceutical Manufacturers Association, 1411 K Street, N.W., Washington 5, D.C.

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